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PRE-EMPHYSEMA IN CHILDREN
Its Recognition and Treatment

ROY F. GODDARD, M.D.
Albuquerque, New Mexico

PULMONARY emphysema has been classified according to etiologic factors and clinical forms,[1] and a physiopathologic basis.[2] In June of 1958 the first symposium on Emphysema, held in Aspen, Colorado, ended with no agreement as to the cause of pulmonary emphysema.[3] In June of 1960, a panel of chest physicians[4] suggested a simplified definition of emphysema, with emphasis on the physiologic mechanisms leading to its production; namely, (1) obstruction, (2) hyperaeration, and (3) destruction. Figure 1 represents an artist's sketch of these physiologic impairments leading to full-blown emphysema. It is true that primary emphysema, encompassing these three factors, obstruction, hyperaeration and destruction, does not exist in childhood. Secondary emphysema, resulting from chronic respiratory afflictions in children, may result from such conditions as asthma, bronchiectasis and mucoviscidosis (Fig. 2). We believe that pre-emphysema (or two-thirds of the full-blown picture; namely, obstruction and hyperaeration, without destruction) occurs frequently and can be diagnosed in its early stages and treated effectively before irreversible destruction occurs and hence progression to the full-blown condition. Pre-emphysema, or variously termed mild[5] or temporary or reversible emphysema, is seen in many asthmatic children. It is the intent of this paper to confine the present discussion primarily to the allergic-asthmatic child.

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Dr. Goddard is Director, Pediatric Research Department, Lovelace Foundation for Medical Education and Research, Albuquerque, New Mexico. He is an Associate Fellow of The American College of Allergists.

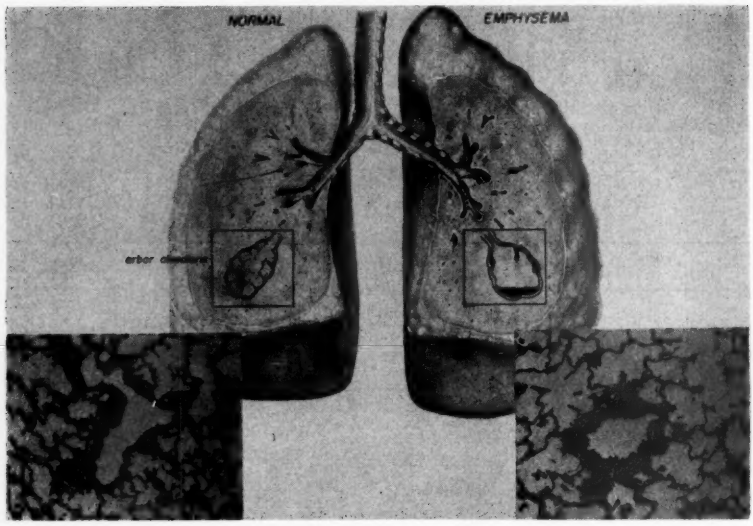


Fig. 1. An artist's sketch of the physiologic mechanisms producing emphysema.

RECOGNITION OF PRE-EMPHYSEMA

The recognition of early emphysema in children is based on subjective findings, including the history (symptoms) and physical examination (general appearance, thoracic configuration, thoracic measurements, type of respirations and percussion and auscultation of the chest). Objective studies, including x-rays of the chest and pulmonary function tests, support the clinical diagnosis.

Clinically, in the pre-emphysematous child, there is usually dyspnea on exertion. Often, a history of cough occurs prior to the onset of the dyspnea. Interference with movement of air out of and, to a lesser extent, into the lungs is many times accompanied by wheezing or other allergic manifestations. On physical examination, the child may be considerably smaller in stature and development than is normal for his age. The thoracic configuration may show an increase in the A-P diameter with a round shoulder or bulging or barrel-chest appearance. Frequently in the earlier stages, there may simply be an increase in the aeration at the bases of the thorax. Thoracic measurements may be helpful; these consist of the following measurements: (1) from the tip of the xiphoid process to a line dissecting the lower thoracic cage; (2) and (3) from the left and right nipples respectively to the lower thoracic cage; (4) the circumference at the nipple line and (5) the A-P diameter. Preliminary studies indicate that such measurements may be helpful in early diagnosis of the reversible emphysema process. It is important to note evidence of expiratory distress

as well as the color, the vigor, the alertness and fatigue of the individual. Frequently, sounds of the breath may be diminished or there may be numerous expiratory wheezes throughout. The bases of the lungs may be hyper-resonant; there may be scattered areas of increased tactile fremitus.

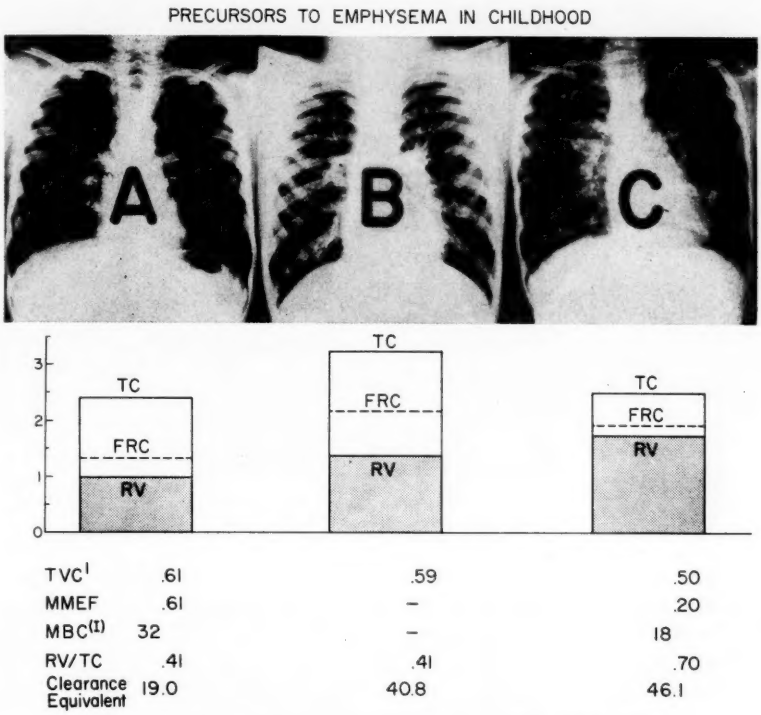


Fig. 2. The ABC's (precursors) of emphysema in childhood.

Objectively, one can study infection and/or allergy present by means of a blood count, a nasal smear, a throat culture, allergenic skin tests, protein electrophoresis, and sinus and chest roentgenograms. Many times the roentgenologist who becomes alerted to reading the x-rays of asthmatic children may interpret the roentgenogram as showing hyperaeration, particularly at the bases in the frontal view. This may also be seen in the lateral roentgenogram, although there may be no significant increase in the anteroposterior diameter (Fig. 4). Such roentgenograms of pre-emphysematous patients are in contrast to the chest roentgenograms of an asthmatic with far-advanced emphysema, showing the typical barrel chest, increase in the A-P diameter, and, in addition, cor pulmonale and evidences of pulmonary hypertension (Fig. 5).

Physiologically, these children show an absolute and relative increase in residual volume, an increase in the work of breathing, and marked diminution in ventilatory, gas mixing, and diffusion capacities. Various methods of study and ventilatory measurements can be obtained in all pediatric age

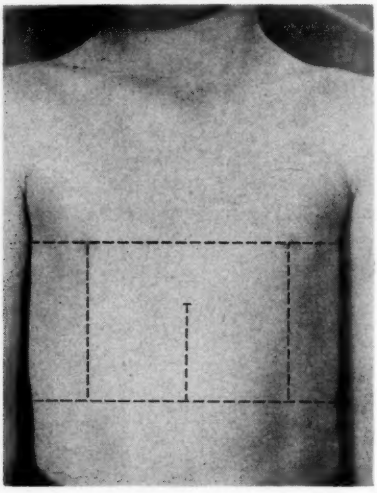


Fig. 3. Thoracic configuration in early emphysema.

groups.[6] Obstruction can be seen rapidly by pneumotachographs, which serve as a rapid screening evaluation, with determinations of peak inspiratory and expiratory flow, the length of exhalation, and the time interval from the peak of inspiration to the peak of expiration (Fig. 9). Forced vital capacities, previously termed timed vital capacities, are of considerable importance in determining obstruction. Perhaps the first second forced expiratory capacity (FEC_1) is the most important, because many times a three-second value cannot be obtained in smaller children. These may be the most accurate determination of obstruction, since many children with severe pulmonary disease are unable to perform a maximum breathing test. Maximum mid-expiratory flow values[7] have been determined however, on a number of children, as have flow-volume contour studies during inspiration and expiration.[8] Maximum breathing capacities, when done, can be of significant help in determining obstruction. Restrictive impairment can be assessed by studying the total capacity, the vital capacity and the residual volume as well as the relation of RV/TC as compared to predicted normal values. Functional impairment is determined by studies of intrapulmonary mixing and distribution undertaken at the time of measuring the functional residual capacity. The ratio of the volume or ventilation required to clear the lungs of nitrogen to the volume being ventilated

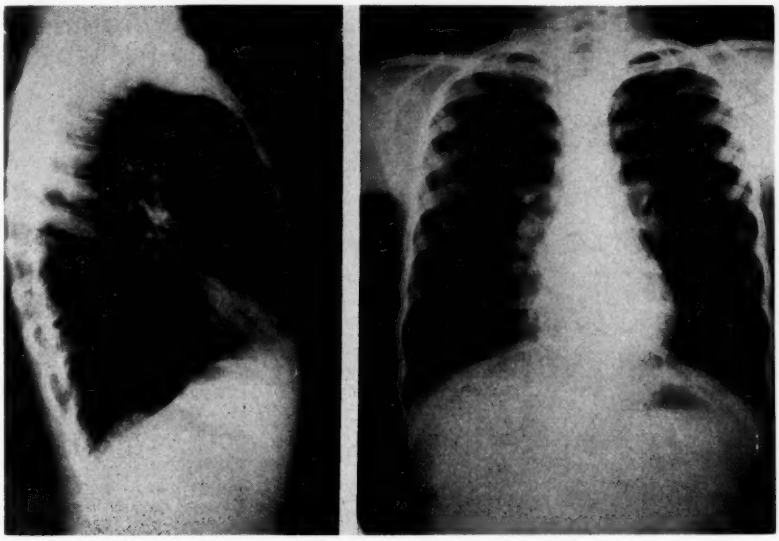


Fig. 4. Chest roentgenograms of asthmatic patient with pre-emphysema (P.M.).

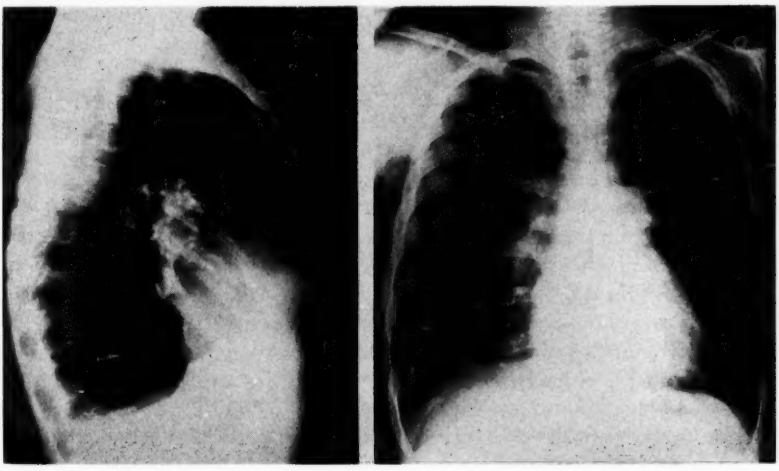


Fig. 5. Chest roentgenograms of asthmatic patient with emphysema (G.B.).

(FRC) gives an indication of the efficiency of ventilation of the nitrogen clearance equivalent.[9] In many instances, these tests may be more important than the spirometric determinations in children. This test allows comparisons either between those with different lung volumes or in the same child whose lungs have changed as the result of growth.

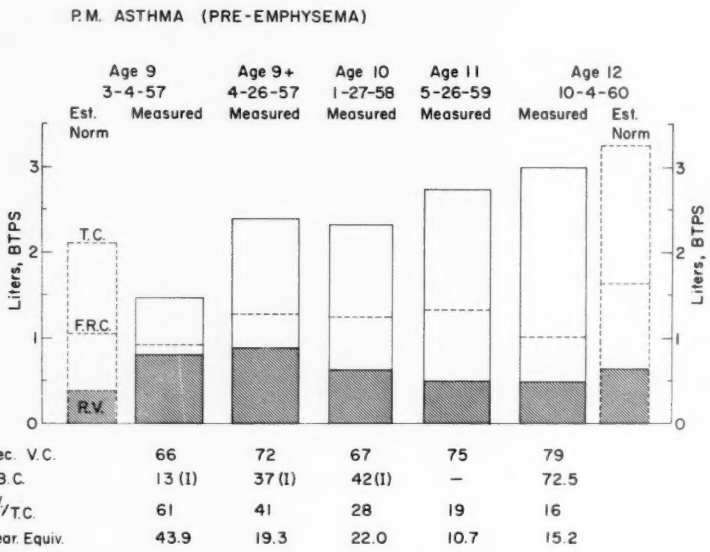
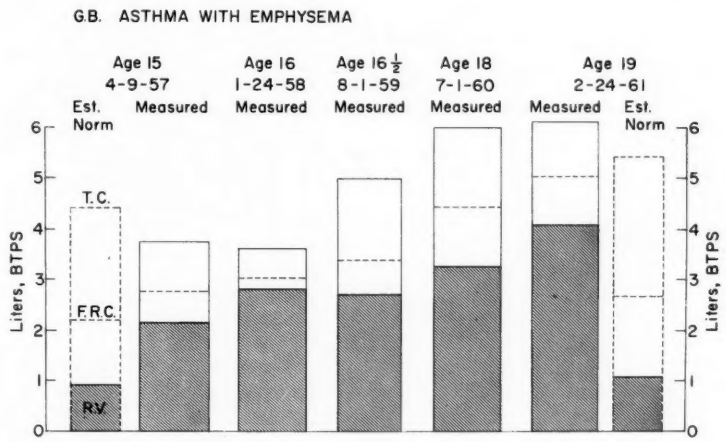


Fig. 6. Pulmonary function studies in asthmatic patient with pre-emphysema (P.M.).

Such studies of obstruction, restriction and functional impairment are summarized (Fig. 6) in a twelve-year-old girl with asthma, who has been followed for three years. When first seen on March 4, 1957, at the age of nine, she was unable to attend school because of severe respiratory distress, evidenced by obstruction with a one second timed vital capacity of 66, an MBC of 13, together with marked restrictive impairment, noted by a vital capacity of 33 per cent, an RV/TC ratio of 61 per cent, and poor ventilatory efficiency, with a nitrogen clearance equivalent of 43.9. Her progress over the past three years has been followed by periodic pulmonary function tests. It can be seen that reversal of volumetric and functional impairment has occurred so that at the time of her last test on October 4, 1960, her one second timed vital capacity had increased to 79; RV/TC was down to 16, and her clearance equivalent was very good. This child is carrying on normal activities and attending school, and falls into the reversible, or temporary or pre-emphysematous category. Treatment has been primarily physiologic (see "Treatment in Early Emphysema . . .", p. 745).

In contrast, a nineteen-year-old male asthmatic patient with emphysema (Fig. 7) does not exhibit this reversibility, but shows progression with probable destruction ensuing. This patient developed asthma at the age of one year, suffered from poliomyelitis at the age of seven years, with a resulting asymmetry of the chest. Regular measures for the treatment of



1 sec. V.C.	38	31	31	26	28
M.B.C.	—	—	21.7	27.0	20.8 (1)
R.V./T.C.	57	77	56	55	67
Clear. Equiv.	51.1	46	32.2	33.1	—

Fig. 7. Pulmonary function studies in asthmatic patient with emphysema (G.B.).

asthma were unsuccessful. The patient moved to the West, where some relief was achieved initially. Emphysema was apparent clinically when first seen at the age of fifteen years. His pulmonary function tests have continuously indicated obstruction as shown by a one second timed vital capacity of 26 to 38, an MBC which has ranged from 21 to 27, and a maximum mid-expiratory flow rate of 0.36 L/sec.; restrictive impairment has been demonstrated by a low vital capacity, ranging from 21 to 59, and an RV/TC of 57 to 77. Extremely poor ventilatory efficiency persists, with a nitrogen clearance equivalent which has ranged from 32 to 51. We believe this chart depicts progressive disease in this patient which, in contrast to the preceding case, should be classified as full-blown emphysema with irreversible destruction.

The above cited cases depict the so-called perennial type of asthma, whereas the seventeen-year-old boy, whose pulmonary function is plotted in Figure 8, shows the seasonal patient, with reversible emphysema or a temporary acute emphysematous situation. This boy does well throughout the year until the spring months when the grasses and trees peculiar to this

area begin to pollinate. As seen in his pulmonary function test, he has considerable obstruction as denoted by a one-second timed vital capacity of 48, and an MBC of 40; restrictive impairment is present with a vital capacity of 70 and an RV/TC of 43; his clearance equivalent shows very poor ventilatory efficiency. Over a six-week period, he showed reversibility

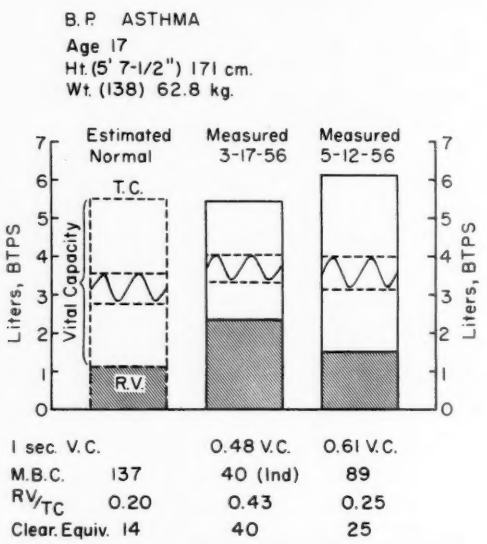


Fig. 8. Pulmonary function studies in seasonal asthmatic patient with reversible emphysema (B.P.).

back toward the normal. Subsequently, in the year 1957, similar findings occurred. In the years 1958-1959, he was away at college and did moderately well. He is living in Albuquerque again this year, and recently he had almost the identical findings as in 1956.

The seasonal asthmatic patient is not beset by the problem which faces the child afflicted with perennial chronic irritation. In Figure 2, Precursors to Emphysema in Childhood, it might be pointed out that the asthmatic child (A) has considerable evidence of obstruction with a TVC of 61, an MMEF of 0.61 L/sec.; an MBC of 32; restrictive impairment with a RV/TC of 41, and a nitrogen clearance equivalent which does not show any appreciable ventilatory impairment. These children can frequently be prevented from developing the full-blown picture of emphysema. The bronchiectatic child (B) shows similar findings with additional ventilatory impairment. Lobectomy of the bronchiectatic areas improved the clinical, as well as the physiological status in this patient. The child with cystic fibrosis or mucoviscidosis (C) shows obstructive, restrictive, and ventilatory impair-

ment with a very high RV/TC of 70, and a high clearance equivalent. The majority of cystic fibrosis patients have irreversible emphysema with destruction and constant infection.

Frequently, we are asked whether there are tests that we can do simply which will show the response of a child to bronchodilators and inhalational

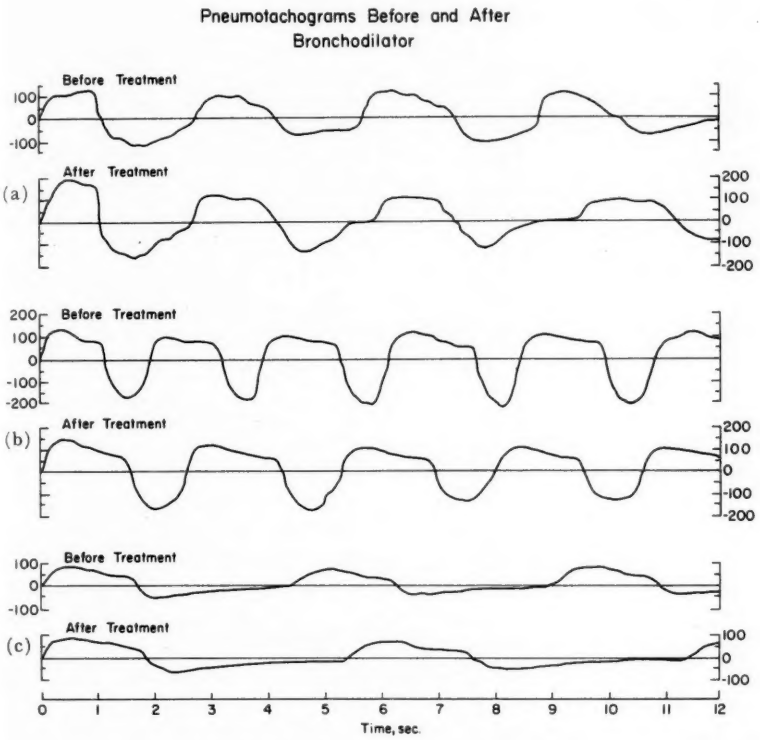


Fig. 9. Pneumotachograms before and after bronchodilator; (a) asthmatic patient with pre-emphysema (P.M.), (b) asthmatic patient with emphysema (G.B.), (c) mucoviscidosis with emphysema (B.O.).

therapy, and whether or not these conditions are reversible. In our management of children with chronic respiratory diseases under periodic follow-up, each child receives at the time of each examination a pneumotachograph tracing before and after therapy. Such tracings indicate the change in the spontaneous breathing pattern before and after inhalation therapy. In Figure 9, such pneumotachographs on the patient P.M., with asthma and pre-emphysema indicate that recently (age twelve), this patient was able to increase the actual inspiratory and expiratory flow volume, as well as the tidal volume exchange, and to decrease the exhalation time, with

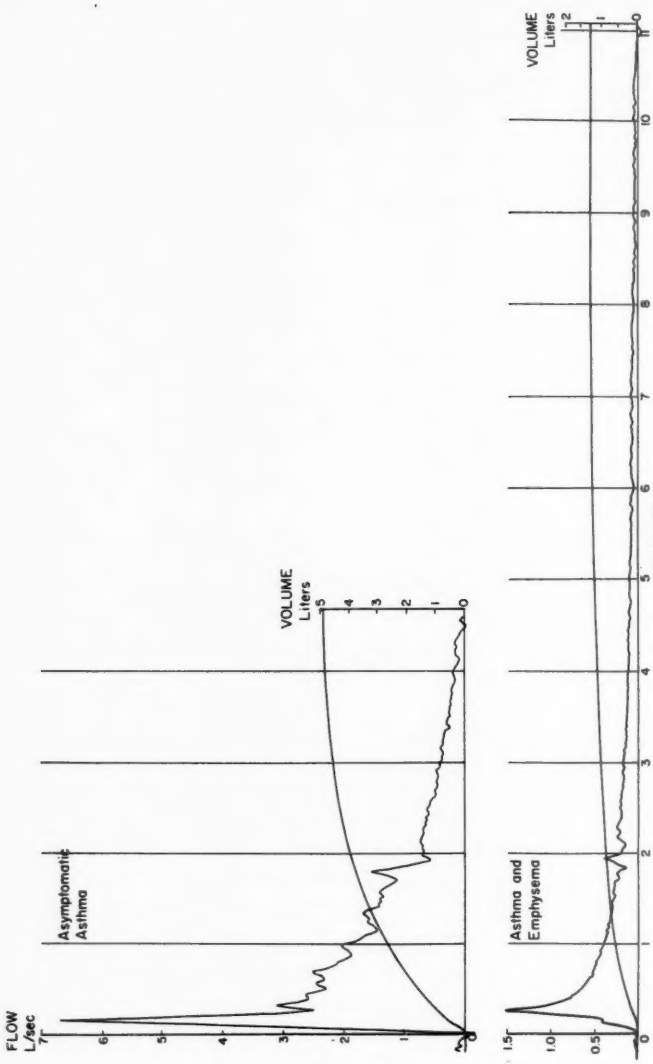


Fig. 10. Flow-pressure contour studies in asymptomatic asthmatic patient (T.H.) vs. asthmatic patient with emphysema (G.B.).

a shortening of the time interval between the peak inspiratory and peak expiratory flows. The patient G.B., with asthma and far-advanced emphysema at the age of nineteen, was able to show some improvement, although this was not as much as was seen in the asthmatic child with pre-emphysema. The third patient, B.O. (age fourteen), afflicted with cystic fibrosis and emphysema, did not show as significant an improvement as the other two patients. Miller has proposed a simple half-second expiratory capacity test in which a single maximum expiratory effort can be used in studying the nature and extent of ventilatory insufficiency.[10] This test can be applicable to even seriously debilitated patients, who cannot perform the maximum breathing capacity test, and is therefore of considerable import. Serial studies furnish an informative method of following the change in ventilatory function during the course of the disease or from therapy. The maximum mid-expiratory flow test determines the flow rate over the mid-half of the forced expiratory vital capacity curve. In patients with pulmonary emphysema, there may be a sudden sharp decrease in the air flow shortly after the initiation of forced expiration. Such was the case in patient G.B., with an MMEF of 0.36 L/sec. This is in contrast to a more normal MMEF of 2.29 L/sec. in J.H., (age fifteen), an asthmatic pre-emphysematous patient.

Flow-volume contour studies offer a method to measure small increases in the expiratory flow resistance in detecting early disease of the bronchial tree. These simultaneous measurements of the expiratory flow, together with the volume during an expiratory phase, help to separate the patient with reversible pulmonary obstruction from the irreversible patient. In the patient G.B., the flow in L/sec. is considerably reduced, and the total volume in liters over the time interval during which forced vital capacity in the expiratory phase occurs is considerably less in contrast to that of a nineteen-year-old male asymptomatic asthmatic patient in the upper tracing (Fig. 10).* The effectiveness of a single inhalational treatment can then be determined by repeating these flow-volume contour studies. In the case of G.B., there was considerable improvement in the total volume which could be moved during one expiratory phase. This volume was increased by approximately 30 per cent. The increase was spread out not only through the first portion of the expiratory phase but also through the latter portion as well. In contrast, the patient B.O., with cystic fibrosis, showed the maximum increase in the early phase of expiration, indicating minimal effect in relieving obstruction in the smaller, more terminal air passageways.

TREATMENT OF EARLY EMPHYSEMA IN CHILDREN

The treatment of early or pre-emphysema in children can be subdivided into (1) correction of the physiological impairment and (2) the accepted general and specific measures utilized in the past in the treatment of pul-

*Flow-volume contour studies to be published at a later date.

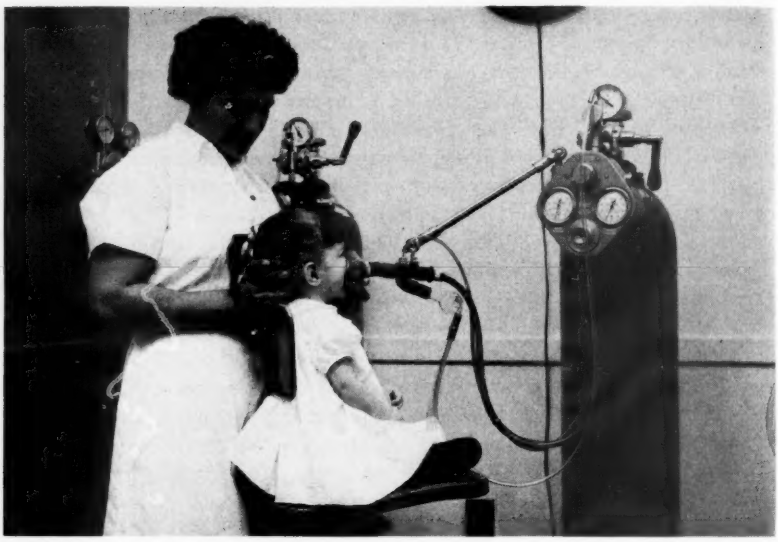


Fig. 11. IPPB administration to two-year-old patient with pre-emphysema.

monary and allergic conditions. In the majority of instances, adequate drainage of bronchi and bronchioles with improved ventilation is required as the initial step. We believe that bronchial hygiene encompassing bronchial dilatation, liquefaction of secretions, reduction of irritation and edema of the bronchial walls, and control of infection, can do much towards the prevention of permanent obstructive, restrictive and functional impairment of the lungs. This we do by giving inhalation therapy as previously outlined.[11]

Physiologic therapy includes respiratory exercises, if cooperation can be satisfactorily attained, and the use of intermittent positive pressure breathing treatments (IPPB). Children from one to five years of age use the Bennett IV-4P or IV-3C pressure breathing unit, modified from the TV-2P adult model. Slow, deep breathing is desirable in order to avoid hyperventilation. As the child becomes adjusted to the positive pressure breathing technique, an aerosol mixture should be introduced through the nebulizer. These aerosols usually consist of four types: (1) bronchodilators, (2) antibiotics, (3) detergent or wetting agents or anti-foam solutions and (4) digestive enzymes. Initial pressures of 8 to 10 cm. may be increased to 10 to 15 cm., depending on the age of the child and the response to treatment (Fig. 11). Initial treatments range from five to ten minutes. Most routine treatments are of ten minutes' duration; occasionally, some may be increased to twelve minutes. The TV-2P Bennett therapy unit is used in asthmatic children over the age of six years for giving inspiratory positive pressure breathing (IPPB). The frequency of treatments depends on the acuteness and severity

of the condition and the progress of the child. A child with status asthmaticus may be treated two or three times daily with gradual reduction in the number of treatments as his condition improves. Eventual bronchial hygiene and/or prophylactic inhalation therapy may be given at weekly or monthly intervals as the patient's clinical and physiological status warrants.

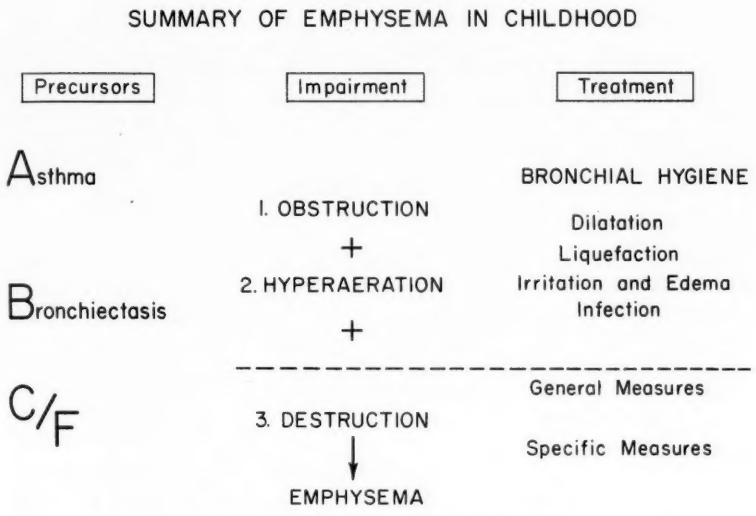


Fig. 12. Summary of emphysema in childhood.

Supportive therapy includes desensitization with allergenic extracts where definite allergies have been proved, and/or periodic cold or flu immunizations in children whose asthmatic attacks are precipitated by colds. General measures concerning diet, clothing, fatigue, environment, irritants and immediate treatment of respiratory infections must be included in this respiratory therapeutic regimen.[12] Gamma globulin may be helpful in those children with hypogammaglobulinemia, associated with chronic respiratory conditions. There is a place for the use of steroids in asthmatic children during acute stages. Occasionally, the combination of a tranquilizer and a steroid may be of considerable value. Bronchoscopy has proven to be lifesaving many times in acute situations. Physiotherapy and breathing exercises can be of considerable benefit in older children. Psychotherapy often contributes greatly in those cases with an emotional background. Specific measures, as utilized by all of us, are indeed a vital part of the regimen. With the better understanding of bronchopulmonary diseases in children will come earlier diagnosis and treatment. Not only will lives be saved, but the progression to chronic respiratory invaldism at a later age may be prevented.

SUMMARY

In Figure 12, we have summarized emphysema in childhood, simplifying the definition of emphysema on a physiologic impairment basis, as including (1) obstruction, (2) hyperaeration and (3) destruction. When only obstruction and hyperaeration are present, we believe this can be classified as pre-emphysema, or transient or reversible emphysema. If the precursors of emphysema in childhood, such as asthma, bronchiectasis and cystic fibrosis of the pancreas (mucoviscidosis), are treated intensively at an early stage, one may be able to prevent full-blown secondary emphysema from occurring. Treatment should be designed to correct the physiologic impairment. This can be done by bronchial hygiene, aimed at bronchial dilatation, liquefaction of secretions, reduction of irritation and edema of the bronchial walls, and control of infection, together with supportive therapy including the basic and specific measures, which have been utilized in the past.

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THE CESSATION OF RAIN

Although the amount of pollen gathered was always lessened by a fall of rain, this decrease, as might naturally be expected, was generally compensated for soon after the cessation of rain; and this was always the more marked if with the cessation of rain there had been a rise in the temperature.—Hay Fever: It's Causes, Treatment, and Effective Prevention, C. H. Blackley, M.D., Baillière, Tindall and Cox, London, England, 1880.

PNEUMOMEDIASTINUM AND SUBCUTANEOUS EMPHYSEMA COMPLICATING BRONCHIAL ASTHMA IN CHILDREN

A Report of Four Cases

JOHN P. McGOVERN, M.D., F.A.C.A., EDWARD B. SINGLETON, M.D., KEMAL OZKARAGOZ, M.D., and ALBERT E. HENSEL, JR., M.D.
Houston, Texas

THOMAS G. JOHNSTON, M.D., F.A.C.A.
Little Rock, Arkansas

A REVIEW of the American and foreign medical literature of the last 100 years (through January 1960) yields twenty documented cases of mediastinal and/or subcutaneous emphysema complicating bronchial asthma in children.[1] In all except two of these children, conservative therapy was successful; needle aspiration in one and surgical intervention for removal of mediastinal air in the other aggravated each. In addition to these twenty cases from the literature, we recently reported in detail the case of a twenty-seven-month-old infant, the youngest reported with this complication of asthma.[1] Also since our review, two additional reports of emphysema in children (eight years old and nine years old respectively) have been published.[2,3]

We believe that this symptom-complex in children is much more common than is generally supposed, that it is frequently overlooked and/or misdiagnosed and incorrectly treated.

This report adds four additional cases in children that we have seen over the past eight years, outlines the salient diagnostic features and methods of management, and summarizes briefly the probable mechanisms of production.

CASE REPORTS

Case 1.—A twelve-year-old girl (D.G.) was admitted by her pediatrician to Texas Children's Hospital with a diagnosis of severe asthma and the complaint of marked substernal pain. Two days before admission to the hospital, she had an "upper respiratory infection with low-grade fever." The next day she coughed, wheezed and became dyspneic. Severity of symptoms progressed. The following morning her physician prescribed Isuprel® spray and Achromycin®; that night she complained of marked shortness of breath and substernal pain, aggravated by coughing on deep inspiration. On the morning of admission she received intravenously 100 mg of aminophylline in 4 cc diluent.

Her childhood was uneventful until the age of six years, when she developed an "allergic cough," which apparently progressed in intensity until she was nine years old. Then, in addition to episodes of paroxysmal coughing, she began having periodic asthma. There was no family history of allergy.

Examination at time of admission revealed a well-nourished, well-developed girl who was restless, apprehensive, and dyspneic. There was flaring of her nares,

From the Departments of Pediatrics and Microbiology, Baylor University College of Medicine, Houston, Texas; and the Department of Medicine, University of Arkansas School of Medicine, Little Rock, Arkansas.

marked retraction of lower intercostal spaces and retraction substernally. Her temperature was 98.4 degrees F orally; pulse rate 140 per minute; respiratory rate 48 per minute; and blood pressure of 130 systolic and 90 diastolic. Her nasal mucosa was pale and swollen. There was moderate hyperemia of the pharynx and ton-

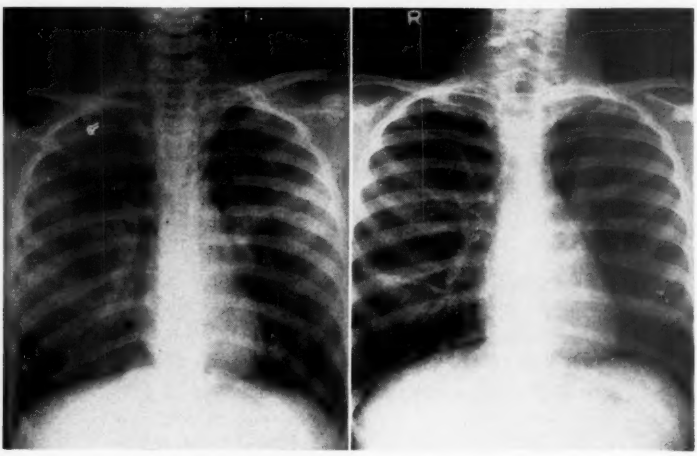

Fig. 1. Case 1. D.G. *(left)* Portable chest x-ray. *(right)* Repeat Anteroposterior of chest.

sillar tissues were hypertrophic. No significant local or generalized lymphadenopathy was noted. Chest configuration was increased in the anteroposterior diameter. Hyperresonance was noted by percussion of chest; auscultation revealed diminished breath sounds and many expiratory wheezes and fine râles bilaterally. The heart border seemed contracted by percussion; rhythm was regular, although sounds were distant, and no murmurs were heard. A "crackling" sound synchronous with the heart beat was heard over the precordium. Skin turgor was poor. There was moderate acrocyanosis. Swelling and crepitation by palpation were noted in the neck, markedly over the right side. Remainder of physical examination was within normal limits.

Laboratory Findings on Admission.—Urinalysis revealed four to six white blood cells per cubic millimeter in a centrifuged specimen; absence of sugar, albumin and acetone; pH of 4.5; and specific gravity of 1.005. Blood studies at admission showed 7,250 white blood cells per cubic millimeter, with a differential count of 2 per cent stab forms, 51 per cent polymorphonuclear leukocytes, 37 per cent lymphocytes, 1 per cent monocytes and 9 per cent eosinophiles. Hemoglobin was 13.1 per cent, with hematocrit of 44 per cent. Blood serology was negative. Patch test for tuberculosis was negative at forty-eight and seventy-two hours.

Roentgenograms at the time of admission were interpreted as showing questionable minimal pulmonary emphysema without evidence of subcutaneous and/or mediastinal emphysema. The lung fields were clear; there was no pneumothorax.

Course of Illness.—The patient was placed in oxygen with head and chest elevated, given Nembutal® ¾ grains orally, and Achromycin® therapy was continued. During the night cough and dyspnea increased, with progression of subcutaneous

emphysema by palpation. The attending pediatrician then administered one-half grain codeine intramuscularly and 250 mg of aminophylline intravenously, which was repeated once to control respiratory difficulty. Administered intravenously was 250 cc of 5 per cent glucose in Lactate Ringers, followed by 500 cc of 5 per cent glucose in distilled water.

The next morning she continued breathing with maximal respiratory effort—respiratory rate of 64 per minute and pulse rate of 140 per minute. Auscultation of the chest revealed intense and widely distributed inspiratory and expiratory wheezes and "bubbling" râles. "Crackling" over the precordium, synchronized with systole, was diminished but still heard. Percussion notes remained hyperresonant. Subcu-

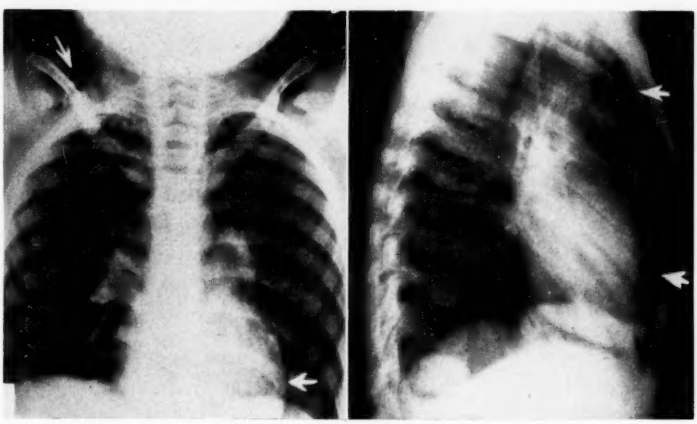

Fig. 2. Case 2. J.T. *(left)* Anteroposterior chest x-ray. *(right)* Lateral chest x-ray.

taneous emphysema of the neck had increased. Roentgenograms (Fig. 1) were repeated and showed slight extension of emphysema, involving the neck and superior mediastinum. There was no x-ray evidence of pneumothorax or pneumonitis and but questionable minimal pulmonary emphysema. Intravenous aminophylline again was given, resulting in some lessening of cough and wheezing. Vomiting ceased and she was able to take fluids orally. A regime of three deep inhalations from a nebulizer containing 1:100 isoproterenol HCl solution was instituted once every hour when she was awake. Thorazine® 10 mg four times a day and Chlor-Trimeton® 8 mg every 12 hours were started.

Steady and rapid improvement followed, so that three days later there was no asthma and chest radiographs showed complete resolution of mediastinal and subcutaneous emphysema.

During the next several years this patient had symptoms of perennial allergic rhinitis and intermittent attacks of asthma, but there was no recurrence of mediastinal or subcutaneous emphysema.

Case **2.** A seven-year-old boy (J.T.) was admitted to the hospital with major complaints of sudden pain in the upper back, "swelling of the neck," and marked respiratory distress. Persistent wheezing and dry cough of three days' duration had preceded these acute symptoms.

He had had "eczema" in infancy which cleared spontaneously; this was followed by the onset of asthma at three years of age. Skin tests were positive to several in-

halant allergens which had been suspected clinically, and avoidance measures were instituted.

At time of hospital admission he appeared well nourished and well developed, but in acute distress. Temperature was 99 degrees F orally, pulse rate 100 per minute and respirations dyspneic at 20 per minute. Subcutaneous crepitation was easily palpated over the right side of the neck and upper chest. Expiratory wheezes were heard

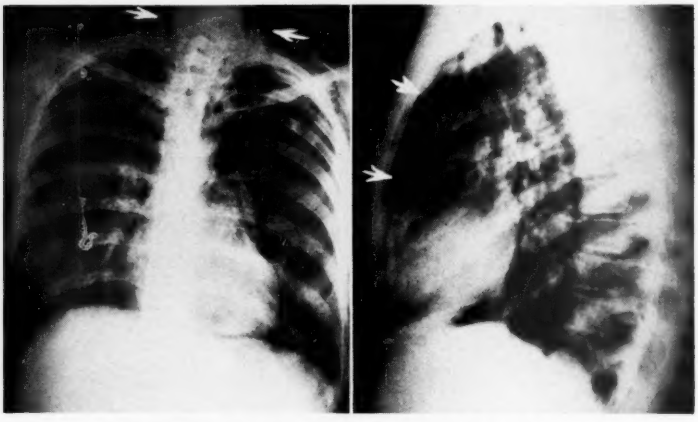

Fig. 3. Case 3. J.B. *(left)* Anteroposterior chest x-ray. *(right)* Lateral chest x-ray.

bilaterally; hyperresonance was noted by percussion. Cardiac rhythm was regular, no murmurs were heard and the heart silhouette seemed within normal limits by percussion.

Laboratory Findings on Admission.—Complete blood count and urinalysis were within normal limits. Posteroanterior radiographs of chest showed moderate mediastinal emphysema between pericardium and pleura. Extension of emphysema into subcutaneous tissues of neck had also occurred. Lateral views showed extensive accumulation of air in anterior and superior portions of mediastinum. These changes may be seen in Figure 2.

Course of Illness.—The child was placed in oxygen with mist and was given therapy to effect bronchodilation, sedation, and hydration.[4] His condition improved rapidly, so that by the next day dyspnea had subsided and clinical signs of emphysema were disappearing.

Shortly thereafter he had a complete allergic survey, received hyposensitization to the offending airborne allergens, and has remained asymptomatic except for mild episodes of asthma.

Case 3. A twelve-year-old girl (J.B.) was first seen with the complaint of swelling over the right side of the neck following a severe attack of asthma. The child stated, "I had the feeling of beads under my skin just like this one time before," which would indicate that she may have had subcutaneous emphysema at some time in the past.

Examination revealed crepitation of subcutaneous tissues of the right side of the

neck. Expiratory wheezes were heard over the entire chest; heart sounds were regular and there were no murmurs.

Anteroposterior radiograph of chest showed extensive mediastinal emphysema with extension into soft tissues of neck and axillary region. Lateral view showed more clearly collection of air in anterior portion of mediastinum. These findings are shown in Figure 3.

Course of Illness.—Asthma was controlled by bedrest, Aminet® suppositories and Adrenalin as needed. Clinical evidence of subcutaneous emphysema gradually subsided during the next five days. There was no recurrence of emphysema during the next eleven months, at the end of which time she moved to another city.

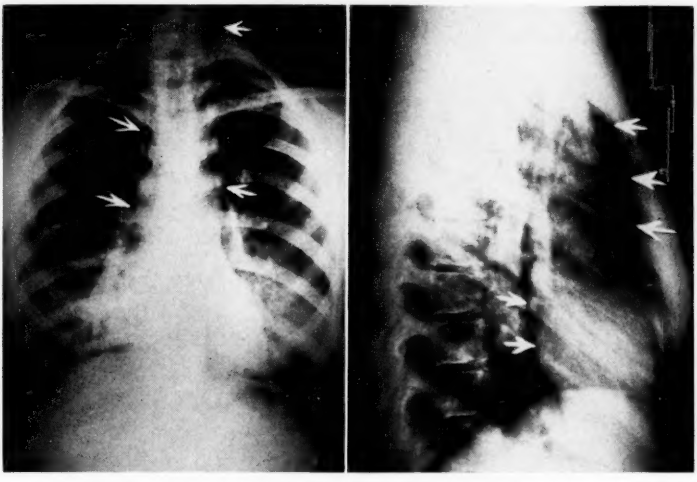

Fig. 4. Case 4. R.H. *(left)* Anteroposterior chest x-ray. *(right)* Lateral chest x-ray.

Case 4. A twelve-year-old girl (R.H.) was seen as an outpatient with "swelling of neck" of a few days' duration. She had complained of sore throat and marked wheezing three days before and had received aqueous epinephrine 1:1000, with temporary relief. This child had had polycyclic attacks of asthma since the age of six years.

Examination revealed a well-nourished, well-developed female adolescent, weighing 106 pounds, 5 ft. 3.5 in. in height. There was moderate dyspnea. Hyperresonance of chest was noted by percussion and copious scattered expiratory wheezes were heard by auscultation. Cardiac findings appeared within normal limits. Remainder of physical examination was not remarkable.

Laboratory Findings in Office.—Vital capacity was 1.6 liters, or 50 per cent of predicted normal. Posteroanterior chest radiograph showed air within mediastinal structures with extension into neck. Lateral view showed collection of air within anterosuperior portion of the mediastinum as well as in posterior areas (Fig. 4).

Course of Illness.—She was placed at bedrest and received potassium iodide and Amodrine® capsules every four to six hours as needed. Subcutaneous emphysema gradually subsided during the next three days and there was no clinical evidence on the fourth day. There has been no recurrence of emphysema.

REVIEW OF CASES

Most children with subcutaneous and/or mediastinal emphysema complicating asthma reported in the literature,[1] as well as those in this series, demonstrated a triad of symptoms—swelling of the neck, wheezing, and marked respiratory distress. Chest pain and cough were reported in some patients. In addition to wheezing in our four patients, three complained of

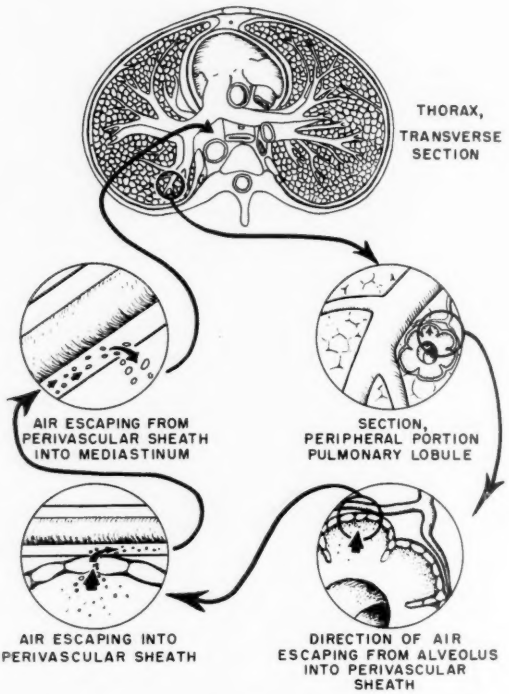

Fig. 5. Schematic illustration of the development of mediastinal emphysema.

swelling of neck, two of marked respiratory distress, one of severe retrosternal pain aggravated by deep breathing, and one of pain in the back. One child in our series, D.G., was found to have Hamman's sign of pericardial air (a "crackling" sound by auscultation over the precordium).[5] This is the first such case in a child reported in the literature. Roentgenograms, as shown in Figures 1-4, confirmed the diagnosis in each case. There was no instance of pneumothorax associated with subcutaneous and/or mediastinal emphysema in our cases, nor was there in those reported in the literature. Including our cases with those from the literature, seven of the eight teen-age children were girls.

DISCUSSION

The initiating mechanism of production of this complication of asthma probably involves obstruction of bronchi and bronchioles, allowing air to pass distally on inspiration but not to escape past obstruction on expiration. As trapped air increases in volume, increased pressure gradients between alveoli and adjoining vascular sheaths develop, according to Macklin.[6-8] This increased pressure forces air through alveolar walls into perivascular sheaths. Air then migrates up perivascular sheaths into mediastinum, as shown in Figure 5. From the mediastinum air may escape by way of vascular sheaths into several parts of the body, following which, generally, there is considerable relief of pressure symptoms. Salmon and his co-authors[9] described a similar mechanism in infants with "airblock."

Each of our cases improved rapidly with conservative therapy between three to four days after onset. This is in agreement with an analysis of reported cases in that, in general, conservative therapy is the treatment of choice; surgical intervention seems *not* to be indicated.[1]

SUMMARY

Four case reports of subcutaneous and/or mediastinal emphysema complicating asthma in infants and children are added to the twenty-three cases previously reported in the medical literature. A brief discussion of the clinical symptomatology, therapy, and pathophysiology of this complication is given. Conservative therapy, without surgical intervention, appears to be the treatment of choice.

ACKNOWLEDGMENT

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3509 Montrose Boulevard

ASTHMA IN PATIENTS WHOSE SYMPTOMS BEGAN BEFORE SIX YEARS OF AGE

A Review of Fifty-eight Cases

CLAUDE A. FRAZIER, M.D., F.A.C.A.
Asheville, North Carolina

DETERMINATION of the etiology, treatment, and prognosis of severe asthma in the young child can be interesting as well as complicated. It was hoped that this problem might be clarified by a review of the charts of fifty-eight infants and children afflicted with asthma and associated allergies. The children's symptoms began before they were six years of age. The following data were studied and compared: history, physical examination findings, laboratory results, skin tests, etiologic diagnosis, and treatment (both medical or surgical). Follow-up had continued for a minimum of three years. The cases were obtained from the files of Dr. Robert A. Cooke of New York City.

TABLE I. TIME FROM ONSET OF SYMPTOMS TO FIRST VISIT TO ALLERGIST

Elapsed Time	Number of Patients
0-6 months	13
6-12 months	4
1-2 years	12
2-4 years	18
4-6 years	11

The length of time between the onset of asthmatic symptoms and the first office visit was determined (Table I). In twenty-nine patients, or one-half of the total number, the symptoms had been present from two to six years before allergic study. Onset occurred before two years of age in twenty-eight of the patients (Table II). In those whose symptoms had begun before the age of one year, there had been an average delay of three and one-third years from the time of onset to the time treatment was sought. The chief associated allergies in the fifty-eight patients were eczema (thirty-six), nasal allergy (twenty-nine), and urticaria (eighteen).

HISTORY

There was a high incidence of bacterial infections, which usually preceded the onset of asthma, and a large number of these were severe. Twenty-five of the children had a history of pneumonia, pertussis, or tracheobronchitis, while fifty-four had had frequent upper respiratory infections. The parents frequently said that for several months before the onset of asthma the child

had had a croupy cough associated with upper respiratory infections. Other past illnesses included measles, impetigo, croup, pyelitis, and posterior cervical lymph node enlargement.

In twenty-nine cases, the tonsils and adenoids had been removed before the child was seen in Dr. Cooke's office. They had been removed before the age of four in twenty-one. According to the histories, there was slight or temporary improvement of the asthma after this operation without additional allergic study and management.

TABLE II. AGE AT ONSET OF SYMPTOMS

Age (Years)	Number of Patients	Average Time from Onset to First Visit to Allergist (Years)
0-1	8	3.3
1-2	20	1.7
2-4	26	2.2
4-6	4	2.2
Total	58	2.4

Twenty-nine of the children had occasional attacks of asthma (three or four a year), while the other twenty-nine had one or more severe attacks a month. The family history was positive for allergy in forty-nine of the patients, with a positive history on both sides of the family in twenty-one. Behavior problems were noted in only four patients.

PHYSICAL EXAMINATION

On rhinological examination, the mucous membranes were found to be swollen and pale in twenty-nine of the patients, and polyps were present in two patients. Twenty-eight of the patients had slightly inflamed pharynges. The tonsils were markedly enlarged in seventeen, while twenty-nine had had the tonsils removed, as stated above. Ten patients had hypertrophied lymphoid tissue on the posterior pharyngeal wall as well as enlarged lingual tonsils. In thirty-seven patients, the adenoids were definitely enlarged as proved by nasopharyngoscopic examination and lateral soft tissue x-ray of the nasopharynx.

Twenty-seven of the patients had enlarged cervical lymph nodes. Examination of the sinuses, by both x-ray and transillumination, indicated that in twenty-four patients there was a definite thickening of the mucous membranes within the sinuses. One or more of the maxillary antra were involved in all these patients, while in nine the ethmoid sinuses were also involved. The ethmoid sinuses were never involved alone. All patients with sinus involvement also had enlarged adenoidal tissue and enlarged cervical lymph nodes.

Chest examination at the first office visit showed sixteen of the patients to have pigeon breast; twelve, a double Harrison groove; and ten, wheezes and sibilant rales. Heart examination was negative, except for functional apical

systolic murmur in two patients. Some degree of eczema was found in thirty-six patients, and an additional eighteen had dry, rough skin. Two patients were mouth-breathers.

ETIOLOGIC FACTORS

The chief etiological factors were inhalants, foods, and bacteria. Indirect intradermal skin tests were done by passive transfer on all but five patients, and the results were corroborated later by direct skin testing.

TABLE III. REACTIONS TO INHALANTS IN FIFTY-EIGHT PATIENTS

Initial Test

Inhalant	Number Reacting
House dust	53
Ragweed pollen	31
Dog dander	21
Feathers	17
Timothy pollen	16
Mold spores	15
Plantain pollen	11
Tree pollen	8
Sorrel pollen	8
Kapok seed	5
Horse dander	5

Inhalants.—The reactions to the inhalants at the initial test are given in Table III. Only those cases with moderate to marked reactions are included.

Foods.—The presence of food allergy had been suspected in thirty patients. In twenty, clinical tests and direct or indirect skin tests had proved that food was related to some of the allergic symptoms. In those patients who had asthma related to foods, eczema was also present. Peanuts, fish, chocolate, eggs, milk, oranges, and spinach were the foods of chief clinical significance. The principal syndromes were asthma, urticaria, eczema, and angioedema. Other symptoms that were thought to be produced by foods were nausea, vomiting, diarrhea, pruritus, and blotchy skin; the relationships could not, however, be proved. (It is interesting to note that one patient developed asthma whenever he cracked a walnut.) In a total of 2,500 food tests, there were ninety moderate to marked positive reactions.

Bacteria.—Cultures for bacteria were done in all cases: thirty-eight pharyngeal, thirty-six nasopharyngeal, and thirty-two tonsil tissue cultures, with a combination being used in some patients. The results are shown in Table IV. The children yielding hemolytic Staphylococcus in their cultures also had the most severe asthma. Eighteen of the nasopharyngeal and fifteen of the pharyngeal cultures had been done prior to the removal of tonsils and adenoids.

It is interesting to compare pharyngeal and nasopharyngeal cultures with tonsil tissue cultures. Of the fifteen pharyngeal cultures, only four had the

TABLE IV. ORGANISMS FOUND ON CULTURE

Source	Number of Patients	Streptococcus	Pneumococcus	Hemolytic Staphylococcus	Neisseria Catarrhalis	Klebsiella Pneumoniae	Proteus Vulgaris	Hemophilus Influenzae
Pharynx	38	26	17	10	20			2
Nasopharynx	36	28	25	14	7		1	
Tonsil tissue	32	27	15	21	12	1		

same organism as the tonsil tissue. The organisms in eight of the eighteen nasopharyngeal cultures were the same as in the tonsil tissue. Pharyngeal and nasopharyngeal cultures were similar in one instance.

Skin tests to bacterial vaccines were made in sixteen of the patients and read after two days. There were moderate to marked reactions to hemolytic staphylococcus in five patients, to pneumococcus in three, and to hemolytic streptococcus in five.

Drug Allergy.—Ten children had a history of drug allergy, with aspirin and sulfonamides causing the symptoms in most. The other offending drugs were cod liver oil, phenobarbital, and penicillin. The symptoms produced or aggravated were asthma, nasal allergy, urticaria, and eczema. In one case, the parents thought that Provatol caused the asthma, and the sesame oil contained in the drug gave a positive passive transfer test with the child's serum. When the patient was given Provatol under controlled conditions, no increase in the severity of the asthma was noticed.

LABORATORY STUDIES

In ten patients, the hemoglobin levels were below 8 grams per 100 cc at the initial examination. While the total white blood cell count of the fifty-eight did not vary appreciably from the normal, the eosinophil counts varied from 3 to 17 per cent, with an average of 9 per cent.

TREATMENT

Chemotherapy and antibiotics were given as needed for the acute infections, according to the type of bacteria shown in the cultures. Vitamins, food elimination diets, and environmental-control measures constituted the initial treatment. General instructions for asthmatic patients were given, and symptomatic treatment was employed as needed. In the thirty-two patients in which the tonsils and adenoids were removed, vaccines were made from the tissue cultures. In twenty-eight of the thirty-two cases, the operation was primary.

Injections of extracts were given according to the histories and skin tests of the patients. In twenty-three patients, autogenous dust (prepared from

TABLE V. REACTIONS TO INHALANTS: LATER TEST

Inhalant	Greater		Less	
	Number of Patients	Increase (Per Cent)	Number of Patients	Decrease (Per Cent)
House dust	3	6	3	6
Ragweed pollen	3	10	18	29
Dog dander	8	38	6	29
Feathers	9	56	8	50
Timothy pollen	6	37	5	31
Mold spores	1	7	2	13
Plantain pollen	3	9	12	27
Tree pollen	4	50	2	25
Sorrel pollen	2	25	1	12
Kapok seed	1	20		
Horse dander	1	20	4	80
Wool	1	33	1	33

the home sweepings) was given alone or in combination with stock dust. Autogenous bacterial vaccines were given to fifty patients. These vaccines were from tonsil tissue cultures in twenty-five cases, from nasopharyngeal and pharyngeal cultures in twenty-six, and from sinus culture in one. Other bacterial products given were as follows: influenza vaccine, twenty-two patients; Staphylococcus toxoid, thirteen; and stock vaccine (containing several different organisms), fifty-six.

RE-EVALUATION OF PATIENTS AFTER ALLERGIC MANAGEMENT

After three years of allergic management, the patient's condition was re-evaluated. There had been a reduction in upper respiratory infections in most of the children, and a weight gain to a more nearly normal size in those who had been underweight.

Improvement in asthma was slight in two patients, moderate in three and marked in fifty-three. The associated allergies had been somewhat alleviated by means of the treatment of the asthma.

Fifteen of the patients had been admitted to the hospital at some time during the three years for the following conditions: broncho-pneumonia, eight; upper respiratory infection, three; tonsillitis, two; appendicitis, one; and tracheobronchitis, two.

The skin tests to the inhalants were repeated from three to thirteen years after the initial tests. The changes in the reactions are shown in Table V. It is interesting to note the decrease in positive reactions to ragweed and several other inhalants. It was then determined how many of the skin tests which had initially been completely negative later gave positive reactions (Table VI). It was also interesting to see how many of the initially positive skin tests became negative after several years. All patients who gave positive skin tests to the grasses and weeds subsequently manifested seasonal hay fever. It was noted that eight of the patients developed food allergy, while two patients were no longer afflicted with such allergies.

In twenty patients who had had the most severe asthma, cultures were made after several years of treatment with autogenous vaccine. It was

noted that the organisms were still similar to those in the initial culture except in one respect: staphylococcus which had been found in all twenty

TABLE VI. NUMBER OF PATIENTS WHOSE SKIN TESTS CHANGED FROM NEGATIVE TO POSITIVE OR POSITIVE TO NEGATIVE*

Inhalant	−to+	+to−
Dog dander	3	2
Horse dander	0	2
Timothy pollen	7	2
Ragweed pollen	2	1
Plantain pollen	3	0
Mold spores	3	0
Tree pollen	2	0
Sorrel pollen	1	0
Wool	1	1

*There were no such changes in reactions to house dust, feathers, and kapok.

of the original cultures had disappeared in seventeen after autogenous vaccine treatment. These same patients had a marked reduction in respiratory infections and asthma attacks.

COMMENT

It is important to realize that asthma can start early in life and equally important for the physician to be alert to make an early diagnosis. In almost half the fifty-eight cases reviewed here, symptoms began before the patients were two years old.

If there is a history of repeated episodes of upper respiratory infection with wheezing, with or without fever, asthma should be considered an etiologic factor. Some of the indications of asthma in infants are: a family history of allergy, the presence of other allergies (eczema, nasal or drug allergy), and eosinophilia. There is usually a high eosinophilia in infective asthma. Skin tests are usually positive. If asthma is present at the time of examination, sibilant sounds are heard in the chest; these sounds, when scattered over the chest, are as nearly pathognomonic of asthma as any sign can be.[1]

Buffum states that the wheezing, prolonged expiration and musical rales are often absent in infancy. Instead there is a noisy breathing with only moderate dyspnea, and on auscultation, only loud tracheal rales are heard.[2]

The physician cannot positively state that a patient actually has bronchial asthma unless an examination has been made during an attack, even though in most instances a correct diagnosis can be made without examination of the patient and from the history alone.[3]

Kahn states that the prolonged expiratory effort which is typical of the adult asthmatic patient is not seen frequently in young children.[4]

The greatest delay in being studied and treated for allergy was in those

patients whose symptoms of asthma began before the age of one year; this period averaged three and one-third years. An allergic study may be delayed because of a mistaken feeling that a child may "outgrow his allergy." Sometimes asthma in an infant is misdiagnosed as pneumonia, bronchitis, or fibrocystic disease of the pancreas.

Some of the diseases to consider in the diagnosis of asthma in the child are: (1) Foreign Body in the Bronchus, (2) Bronchiolitis, (3) Pneumonia, (4) Bronchiectasis, (5) Croup, (6) Fibrocystic Disease of the Pancreas, (7) Congenital Laryngeal Stridor, (8) Congenital Heart Disease, (9) Thymic Asthma, (10) Sighing Dyspnea, and (11) Nasal Obstruction.

The major etiologic factors were inhalants, food, and bacteria. It was felt that at the time of initial examination bacterial allergy played the largest role. This was indicated by the history of asthma attacks preceded by severe upper respiratory infections. Physical examination also revealed sinus involvement, infected tonsils, and enlarged cervical lymph nodes in many patients. In addition, cultures from the pharynx, nasopharynx, and tonsils seemed to point to a bacterial etiology. A thorough search for foci of infections should therefore be made, and thorough culture studies should be done. In these cases, it seemed that nasopharyngeal cultures gave more accurate evidence of the bacterial flora of the tonsils than pharyngeal cultures alone. Probably both types of cultures should be made.

The Staphylococcus had disappeared from the cultures of seventeen patients between the initial and later studies, and there had been a marked relief of symptoms. It was therefore felt that this organism may play a large part in the etiology of infective asthma. Although skin tests to bacterial toxins were done, they are not of proven value at present.

One should not attempt to treat the asthmatic child by removal of the tonsils and adenoids without benefit of a complete allergic study, since other factors usually play a role.

Sobel concludes that the indications for adenotonsillectomy should be the same for allergic and non-allergic patients, and that the allergy *per se* cannot be considered an indication for tonsillectomy.[5] Furthermore, autogenous tonsil tissue vaccine may be a valuable adjunct in the allergic management of the child.

The chief inhalants were dust, feathers, dog hair, molds, timothy, and ragweed pollen. Allergies in children may change. A child's skin tests may change from negative to positive with the development of clinical sensitivity; therefore, tests should be repeated at intervals. If the physician informs parents of the allergic symptoms that may develop, they will be alerted to bring the child for early treatment if it becomes necessary.

It was felt that foods were not as important in causing asthma in this group of patients as were the bacteria. Skin tests to foods are not as reliable as those to inhalants, and positive food skin tests do not necessarily indicate foods to which the child is sensitive.

With the possible exception of milk, cereals, eggs, fish, and chocolate,

tests with foods are apt to be erroneous.[6] A clinical trial can be said to corroborate skin tests if a food causes asthma in the same time interval on three occasions, and if elimination of the food from the diet brings relief of symptoms.

Emotional disturbances did not seem to be a significant factor in these patients. Anemia was present in a number of patients.

An asthmatic child should be given the benefit of early and complete allergic studies and proper treatment. The latter includes treating the whole child as well as his allergies.

In the routine management of the allergic child, the child should have a well-balanced diet with adequate minerals and vitamins, and the nutritional status should be maintained.[7]

SUMMARY

The histories of fifty-eight children whose asthmatic symptoms began before they were six years of age indicated that there had been a high incidence of bacterial infections, especially of severe upper respiratory infections. In many patients, sinus involvement, infected tonsils, and enlarged cervical lymph nodes were present on examination. Studies of cultures from the pharynx, nasopharynx, and tonsils also seemed to point to a bacterial etiology. The staphylococcus may play a large part in the etiology of infective asthma, since marked relief of symptoms accompanied their disappearance from the cultures of seventeen patients after autogenous vaccine treatment. It is realized that the role of bacterial allergy in infants and children is controversial, as is also the value of autogenous vaccines.

The proper treatment of such a patient requires a thorough study of the child with appropriate allergic measures and re-evaluation at regular intervals.

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Suite 516, City Building

FURTHER OBSERVATIONS ON THE ETIOLOGY OF INFANTILE CORTICAL HYPEROSTOSIS

J. R. BOWMAN, M.D., ROBERT E. PISTON, M.D., and EDWIN A. MEEKS, M.D.

Johnson City, Tennessee

AN INFANT suffering from a disease characterized by hyperirritability, thickening of the bones and painful swelling of the overlying soft tissues was described by Georg Roske, Heidelberg Clinic, in 1930.[1] Clinical studies at that time excluded syphilis, rickets, scurvy, tuberculosis or any other known entity. The clinical picture was that of infantile cortical hyperostosis.

In 1945 Caffey and Silverman[2] described and differentiated a new syndrome which they designated Infantile Cortical Hyperostosis. Since then, the entity has been more readily recognized and seemingly more frequent.[3] Many reports of similar cases have been added to the medical literature.[4-8]

CLINICAL FEATURES

Infantile cortical hyperostosis is a disease peculiar to young infants and has three clinical features common to all patients: *hyperirritability, swellings* of the *soft tissues,* and *cortical thickenings* of the *underlying bones.*[6]

Hyperirritability is present early in the disease and may be of an extreme degree. It may precede the swellings of the soft tissues by a few days or weeks, or else may begin concurrently with them.

Soft tissue swellings appear suddenly near the onset of the disease and are characterized by a painful, tender, wooden or waxy or brawny hardness. The process of swelling occurs deep within the tissues and probably rarely extends outward into the subcutaneous fat or skin. In the early phases, the swellings are exquisitely tender, and although the overlying skin may be slightly warm, it is likely never inflamed or discolored. The membranes beneath the tongue and over the alveolus however, are swollen, tender and are pink when the contiguous and underlying mandible is acutely involved. The swellings begin before roentgenographic changes appear in the underlying bones and involute long before the hyperostoses become invisible to x-rays. They involute without suppuration and without involvement of the regional lymph nodes. The swellings fluctuate in size, and occasionally they recede only to reappear at the original or at new sites. Swellings of the facial and scapular areas have never first appeared after the sixth month of life.

Cortical hyperostoses have involved all the tubular bones of the skeleton. The mandible, scapula, parietal and frontal bones are the flat bones which

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From the Bowman Clinic for Infants and Children, Johnson City, Tennessee.

have been affected. Scapular lesions are said always to be unilateral and have their beginning during the first six months of life. Mandibular lesions never first appear in infants over six months of age; they may be quite extensive.[6]

The mandible, the clavicle and the ulna are the bones most frequently involved. The ulna is the most commonly affected of all the bones of the extremities and may be extensively sclerosed and thickened while its companion, the radius, is normal. Conversely, both of the latter bones can be so acutely and extensively involved that during healing, a synostosis results. Intercostal synostoses also rarely develop when two contiguous ribs are similarly affected.[9] Pleuritic changes with or without effusion occasionally are seen when the overlying ribs are inflamed.[10]

Roentgenography offers the best means of diagnosing the late cases and, by means of x-rays, prenatal cases and bone involvement of prematures at birth have been found.[11]

Other symptoms and signs present during the acute phase in some infants are *pallor, fever, painful pseudoparalysis, pleurisy* with or without effusion and evidences of *nasal* or *bronchial allergy* or other *allergic manifestations.*

While clinical and roentgenographic recovery is usual and complete, several deaths have occurred in patients afflicted with the disease, and at least one death has been directly attributed to it.[8] The hyperirritability usually abates, and the soft tissue swellings subside long before the first six months of life. However, soft tissue swellings and bone lesions in rare instances have been known to persist for five to seven or more years.[6,12]

Common positive laboratory findings in at least some cases are *increased sedimentation rate, increased phosphatase level of the blood serum,* a mild *leukocytosis* with a *relative increase* of the *eosinophils* in the *differential count, positive nasal smears* for *eosinophils* and a mild *lowering of the hemoglobin level.* All other laboratory studies for serologic, viral or bacterial agents have been uniformly negative; all bacterial and viral cultures of tissues and exudates have been sterile.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis must take into consideration acute pyogenic infections of the deep soft tissues, osteomyelitis, scurvy and especially neoplastic bone disease. Confusion of the latter disease with infantile cortical hyperostosis has resulted in needless and mutilating operations on the mandible, the shoulder girdle and the extremities.

PATHOLOGY

In 1957, Eversole, Jr., Holman and Robinson reported:

> . . . that a hitherto undescribed acute inflammation occurs at an early stage of the disease, and that this is associated with the loss of the periosteum and occasionally of the compactness of the subperiosteal layers of the original bone as definite histologic structures. Simultaneously there is a marked fibrous and osteoblastic reaction with much osteoid deposition in the loose fibrous tissue surrounding the bony trabeculae.

This whole process extends out to invade the surrounding soft tissue including the muscle. Therefore the pathological process is intra-periosteal and inflammatory in its early stages rather than subperiosteal and non-inflammatory as the reported cases. Eventually the inflammation subsides spontaneously and the inflamed callus-like process becomes organized into normal trabecular bone which is covered by a thickened periosteum from which scar tissue extends out into the soft tissues. At this *later* stage a subperiosteal cap of lamellar bone, without inflammation, is seen. This is the stage of the disease that has been repeatedly described in biopsies.[13]

Biopsies in late cases have shown edema and thickening of the periosteum with external hyperplasia of the cortex. Specimens taken from the soft tissue swellings have exhibited scattered areas of necrosis in the muscles associated with fibrosis. The arteries and arterioles in the involved muscles may display proliferative changes in the intima.

A significant finding in all cases has been the absence of regional lymph node enlargement as related to the sites of the swellings and hyperostoses.

REVIEW OF TWO PREVIOUSLY REPORTED CASES WITH PROGRESS NOTES

In 1955 some of the authors[12] reported two cases of infantile cortical hyperostosis occurring in infants. The first instance was that of a four-months-old male infant who had had hyperirritability of extreme degree and a tender, massive swelling with wooden or brawny hardness of the tissues about the mandible for two weeks. After evaporated milk was replaced by Mull-Soy, the irritability immediately abated, and the soft tissue swelling rapidly subsided. When milk again was fed, the irritability and swelling recurred. No cortical hyperostoses were demonstrated or ever developed. This infant's mother is afflicted with hay fever and several aunts and uncles on the maternal side suffered from various allergic manifestations. The patient, as he has grown older, has suffered from naso-bronchial allergy, repeated colds and attacks of croup.

The second patient, a six-month-old female infant had hyperirritability and marked swelling and tenderness of the tissues about the jaw for two and one-half months. She had been given heavy doses of chlortetracycline for a protracted period without apparent improvement. After milk and cod liver oil were removed from the diet, all signs and symptoms—except the cortical hyperostosis of the mandible—abated; they recurred repeatedly when the offending allergens were again fed. Since that time, this child has remained well, and the mandibular hyperostosis has disappeared. A younger sibling has suffered from milk allergy, allergic naso-bronchitis and asthma, and a maternal uncle had asthma. The patient's mandible was found to be normal after a recent examination. While she has remained symptom free of nasal allergy, however, the nasal smear was strongly positive for eosinophils.

REPORT OF A NEW CASE

On January 12, 1960, the authors encountered another infant with infantile cortical hyperostosis whose responses to therapeutic measures have shed further light on the etiology and treatment of the disorder.

CASE H.S.S. (Memorial Hospital, Record No. 71403).

History.—This male infant was seen at the age of three months at which time his parents had noted a loss of appetite, irritability, and swelling and tenderness of the tissues about the jaw of six weeks' duration. The infant had been well until the age of six weeks when in addition to evaporated milk, oatmeal, banana, apple sauce, orange juice and Vi-Mix were added to the diet. Within two or three days' time irritability and spitting up of food was followed by swelling and marked tenderness of the tissues of the lower jaw. At the age of seven weeks, Mull-Soy was substituted for the evaporated milk, and all other foods were discontinued. The irritability, spitting of food and swelling subsided, but the mandibular area remained somewhat thickened and swollen.

Fig. 1. Showing the swollen tissues of the mandibular area.

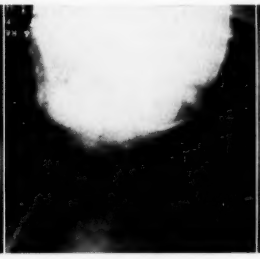

Fig. 2. Roentgenogram showing periosteal and subperiosteal thickening of the mandible and the right scapula. Minimal involvement was noted in the clavicles and other bones.

Fig. 3. Showing the marked swelling and extreme hyperirritability after having been on "the allergic diet" for a period of forty-eight hours.

Pregnancy and Birth Record.—The infant was delivered at full term. The birth weight was 3.18 kg. The pregnancy had been normal and the delivery uncomplicated. During pregnancy the mother had ingested an average amount of milk and had eaten oatmeal on many occasions.

Family History.—Several paternal uncles and aunts had had croup as children, and one uncle had suffered with asthma until he was eight years old; another had had hay fever. On the maternal side, the grandfather had suffered from chronic "bronchial trouble," and several uncles and aunts had had repeated colds all their lives.

Physical Examination.—The three-months-old infant weighed 5.0 kg. Temperature: 37.7 degrees C rectally. He was slightly restless and somewhat pallid. The soft tissues about the lower jaw and upper neck were greatly swollen, moderately tender, warm and of a wooden or waxy or brawny hardness (Fig. 1). The infant cried when the jaws were palpated. The nasal membranes and turbinates were pale and boggy; there was a mucoid nasal discharge. The pharynx was mildly injected. The regional lymph nodes were not enlarged. The examination of the remaining bones showed them to be normal except for a slight fullness and a tenderness over the right scapula and a questionable thickening of the clavicles.

Laboratory Data.—Urine: normal. Hemoglobin 11.5 gm. R.B.C. 4,200,000. W.B.C. 15,000. Differential Count: Lymphocytes 28 per cent, Polymorphonuclear cells 68 per cent, Eosinophils 4 per cent. Corrected sedimentation rate: 20 mm fall in one hour. Alkaline phosphatase 8.5 Bodansky units. Calcium 5.2 mEq. Phos-

phorous 3.5 mEq. Chlorides 108 mEq. Sodium 138 mEq. Urea nitrogen 13 mg per cent. Nasal Smear: 1 + concentration of eosinophils. Skin tests: oats and banana 1 + positive reactions; all other foods gave negative skin reactions.

X-Ray Findings.—"There is marked enlargement with periosteal reaction of the entire mandible with similar changes involving the right scapula, and to a lesser extent, the clavicles and both bones of the leg bilaterally and also both the humerus and femur bilaterally. These findings are consistent with the clinical diagnosis of infantile cortical hyperostosis or Caffey's Disease" (Fig. 2).

Hospital Course.—On the patient's admission to the hospital, the original diet of evaporated milk, oatmeal, banana, orange juice and Vi-Mix, was ordered. Within twenty-four hours there was increased swelling of the cheeks and jaws. By forty-eight hours irritability was marked, and the jaws were more swollen. When seventy-two hours had elapsed, the infant was extremely fretful, slightly feverish, pallid and the cheeks and jaws were greatly swollen and exquisitely tender (Fig. 3). The tissues beneath the tongue were edematous and pink, and the gums were tender and swollen to the degree that the infant refused to nurse the bottle.

The diet was changed to Nutramigen alone and within forty-eight hours, the hyperirritability was gone, the temperature had subsided, the mandibular area was less swollen and tender, and the infant began to nurse and act normally.

After dismissal from the hospital, when the diet was again switched to that consisting of the offending allergens, the symptoms and signs recurred only to subside again on resuming the non-allergic diet. When the offending allergens were offered at six months, no unusual symptoms or reactions occurred and the infant since has remained well except for bouts of mild naso-bronchial allergy.

DISCUSSION

The description of infantile cortical hyperostosis as a disease "of obscure cause and pathogenesis" is an apt one.[6] The etiology has been attributed to viral or bacterial infection although evidences of such agents have been lacking, in that all serologic and bacteriologic tests have been negative, and intensive broad spectrum antibiotic therapy has proven ineffective. Furthermore, with the intensive inflammatory reaction in the acute phase, no local adenopathy has been demonstrated.

Steroid therapy has been used effectively in severe cases affording immediate relief from the acute symptoms and probably has lessened the possibility of later sequellae and deformities.[14] Steroid therapy in young infants carries great risk, however, and is not to be recommended routinely. Such therapy should be reserved only for the seriously ill patient.[7,15]

The etiologic agent must be one to which young infants, even *in utero* in rare instances, are susceptible and one that initiates a disease of variable courses with remissions and relapses. It must be capable of provoking in the host a markedly brawny, edematous, tender, acute inflammatory reaction deep in the soft tissues in seemingly selective sites, notably the periosteum and contiguous structures of the mandibular, scapular and other bony areas. The underlying bone, with its cortex and periosteum disturbed by the acute inflammatory process, responds with the development of a hyperostosis. All of these changes must be reversible because infants so afflicted ultimately recover, in most instances, without scarring or pathophysiologic sequellae.[12]

Of the cases reported in the literature, histories of allergic manifestations have rarely been elicited, and allergy as an etiologic factor has been mentioned only in passing.[16] The authors have not found this to be true in their cases herein reported and in other cases observed but not included in this series. In addition, their patients either have, or later develop, other allergic manifestations in a high percentage of cases, and allergic diseases are prevalent in the family histories. Cases of infantile cortical hyperostosis are now being traced in family trees. Such cases suggest some hereditary factor.[7] Tampas *et al* have found as many as eleven cases in two generations of one family.[3]

The authors propose, therefore, that infantile cortical hyperostosis results from allergic phenomena, wherein the periosteum and cortical bone insulted by an acute and later a chronic inflammatory process, react and heal by the deposition of calcium and bone, a process analogous to, but still somewhat variant from, the healing of scurvy. This is a bone pathology and reaction not previously attributed to allergy.[17] This thesis is supported by the following facts:

1. Infantile cortical hyperostosis is a disease of variable courses affecting infants who are afflicted with or later develop other allergic manifestations.
2. In a majority of cases, the family histories record a frequency of allergic disorders, and recent studies of such cases have uncovered a familial tendency of recurrence and possible hereditary factors.
3. Infectious agents, viral and bacterial, cannot be demonstrated or discovered.
4. The illness is a reversible process, in that recovery is ordinarily complete without residuals.
5. The disease responds dramatically to steroid therapy, and in the early acute phase responds equally as dramatically to the removal of the offending allergens from the diet.

The authors believe and have demonstrated that alteration of the diet—removal of offending allergens—early in the course of this disease in young infants, regardless of how severely afflicted, will result in rapid improvement equal to or surpassing that afforded by steroid therapy! In order for this turn of events to occur, the infant must be seen, diagnosed and treated early, because in late cases when the process is chronic and healing, and after spontaneous desensitization has occurred, no dramatic response can be expected from changing the diet. By this time the infant usually requires no therapy.

SUMMARY AND CONCLUSIONS

The history, clinical features and course of infantile cortical hyperostosis have been reviewed. The progress of two previously reported cases that responded dramatically to the removal of offending allergens from the diet have been recounted. A new patient whose response to dietary therapy fur-

ther substantiates the authors' contention that infantile cortical hyperostosis is the result or healing process of an allergic disease, is discussed. Bone lesions have not been previously attributed to allergic reactions; perhaps other obscure bone conditions in childhood should be restudied in the light of this fact.

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The Bowman Clinic
West Fairview at Boone Street

EVOLUTIONARY THEORY

The most important lesson to be learned from evolutionary theory today is a negative one; the theory shows us what scientific explanations need not do. In particular it shows us that one cannot regard explanations as unsatisfactory when they do not contain laws, or when they are not such as to enable the event in question to have been predicted. This conclusion, which is contrary to the usual view of scientific explanation, has important consequences for research in those subjects in which serious errors are known to arise in the application of the available regularities to individual cases. These subjects include a great part of biology, psychology, anthropology, history, cosmogony, engineering, economics, and quantum physics.—MICHAEL SCRIVEN, "Explanation and Prediction in Evolutionary Theory," *Science*, 130:477, August 28, 1959.

INCIDENCE OF ALLERGIC DISEASES IN A PEDIATRIC PRACTICE IN HONOLULU, HAWAII

W. A. MYERS, M.D.
Honolulu, Hawaii

THE PURPOSE of this survey is to compare the incidence of allergic diseases, especially asthma and allergic rhinitis in children in Honolulu, Hawaii, with surveys on the mainland and elsewhere.

Many of the usual etiologic factors are absent or minimal in Hawaii.[1] Pollen and mold spore counts are low,[2] ragweed is absent, and there is an "ideal" year-round climate with no sudden or marked temperature and barometric pressure changes.[3] The general out-of-door living habits and minimum exposure to house dust should also tend to reduce the prevalence of these conditions. However, in this study and also in the U. S. National Health Survey[4] conducted for twelve months in 1958-1959, the prevalence of "asthma" or "hayfever," or both, on Oahu (City and County of Honolulu) was found to be more than twice the rate on the mainland[5] (Table I). It would therefore seem that some unusual or unknown local condition is an important etiologic factor.

Incidence surveys of allergic disease taken on the mainland in the general population suggest that about 10 per cent or more have or have had one or more of the major allergies (asthma, allergic rhinitis, urticaria and atopic dermatitis) and from 0.5 to 3.0 per cent have been afflicted with bronchial asthma.[6] A questionnaire type of survey conducted in New York State, Connecticut and the city of Montreal, Canada, by Rapaport *et al,*[7] including 5,152 individuals (2,169 under fifteen years of age) listed 12.0 per cent of total and 23.7 per cent of the children under fifteen years as having major allergies. Asthma incidence surveys (Table II) limited to children are scarce.[8] London[9] reported an asthma incidence of 2.3 per cent of 1,500 children in a pediatric practice in North Carolina. Crook *et al*[10] in 1958 found the "incidence" of asthmatic children to be about 5 per cent in a sample of 1,225 patients in a pediatric practice in Tennessee. Kraepelien,[11] in 1950, found the "incidence" in Swedish school children to be 1.3 per cent, based on medical examinations in Stockholm. At Duke University Hospital, 9.3 per cent of 2,951 first visits or admissions on the Pediatric Service were asthmatic in 1955.[8] The highest of these rates is only about one-third of the rate in this Honolulu study.

It was decided to use a sample from our pediatric practice as a means of comparison with the available mainland studies. In order to obtain a trustworthy sample from our files, only children who had been delivered by our Obstetrics Department and followed by our Pediatric Department since birth were included. These records, therefore, represent a complete medical history from birth to their last visit, with monthly or yearly check-

TABLE I. ASTHMA—HAYFEVER* CASES AND PREVALENCE RATES
U. S. National Health Survey

City and County of Honolulu, Hawaii 1958-1959			United States 1957-1958		
Age	Number of Cases	Rate Per 100 Population	Age	Number of Cases	Rate Per 100 Population
Under 15 years	17,500	9.32	Under 15 years	2,060,000	3.96
Under 25 years	23,200	9.42	Under 25 years	3,232,000	4.43
Total all ages	35,800	7.8	Total all ages	8,103,000	4.8

*This group is composed of cases of asthma, asthma with hayfever and hayfever without asthma. "This was by far the most frequent type of chronic condition reported on Oahu (City and County of Honolulu)." Of the total 35,800 cases of all ages, 18,494 were hayfever and 17,293 (48 per cent) were asthma cases.

ups, depending on age as well as all illnesses. They also include consultation records of other members of the group representing twelve different specialties. Thus, many of the inaccuracies of a "past medical history" type of survey obtained from the parents or patients are eliminated. Sample records were selected from groups of equal size and distribution in our alphabetical file of about 20,000 individual records. This method tended to distribute the samples evenly and to prevent including a disproportionate number of any race due to the frequency of certain names characteristic of the Caucasian, Japanese, Korean, Filipino, or Hawaiian races. Siblings are filed together in our pediatric files, but their parents are in a separate adult file. Collecting these data necessitated at least scanning the records of about 5,500 or about 27 per cent of the total records over a period of several years. There are six pediatricians in our group, and we often see one another's patients; so the records do not represent the attitude or interest of any one man. The disadvantages of this method of doing a record survey are that it is time-consuming and cannot be delegated to clerical help. Of advantage is the fact that it can be done at one's leisure in small or large doses and that it is of considerable educational value to the reviewer.

TABLE II. INCIDENCE OF ASTHMA IN CHILDREN

Investigator	Total Population	Source	Asthma Rate*
Kraepelien	?	Swedish school children	1.3
London	1500	Children in N.C. ped. prac.	2.3
Crook	1225	Children in Tenn. ped. prac.	4.7-5.3
Dees	2951	Children at Duke Univ. Hosp.	9.3
Sheldon	2000	Students at Univ. of Mich.	9.0

*Number of asthma cases per 100 of sample population

At times it was necessary for the reviewer to decide whether a diagnosis in the record was correct, or not, in light of later developments in the patient's history, such as response to treatment, later confirmatory diagnoses, sibling histories, laboratory data, and so forth. The reviewer believes that he maintained a conservative policy in the classification of the allergic diagnoses. A correct classification of diagnoses recorded on the child's history card, such as infantile eczema, seborrheic dermatitis, asthmatic bronchitis, bronchiolitis,

wheezing, allergic rhinitis, respiratory allergy, recurrent upper respiratory infections, and so forth, was often difficult, or impossible, especially in infants under two years of age. Some of the minor allergies, such as gastrointestinal, conjunctivitis, tension-fatigue syndrome, and so forth, are not included for this reason. Infantile eczema, atopic dermatitis, and allergic dermatitis are grouped together as "eczema" in order to simplify the diagnosis and to compare with other surveys.

TABLE III. AGE OF ONSET OF ASTHMA IN A HONOLULU PEDIATRIC PRACTICE

Age in Years	Total Cases	Asthma Cases	Per Cent of Age Group
Under 1	215	14	6.5
1	58	14	24.7
2-3	103	42	40.7
4-5	116	20	17.2
6-7	83	13	15.7
8-9	67	5	7.4
10-17	76	4	5.2

The mean age of onset of asthma was 3 years; the extremes were 6 months and 13 years

It is rarely possible to diagnose seasonal hayfever in Hawaii because there are no definite seasons, no accurate pollen surveys, and considerable variation in the pollination times of the grasses, weeds, and trees.[1] However, the allergic children frequently have positive skin tests to local grass pollens, mold spores and mesquite *(kiawe)* pollen.

TABLE IV. AGE DISTRIBUTION IN A HONOLULU PEDIATRIC PRACTICE

Age in Years	Number of Cases	Per Cent of Total
Under 1	215	29.9
1	58	8.1
2-3	103	14.3
4-5	116	16.2
6-7	83	11.6
8-9	67	9.3
10-14	69	9.6
15-17	7	1.0
Total 0-17	718	100

In the Honolulu study, records of 718 pediatric patients with an age range of zero to seventeen years were selected as described above. Two hundred fifteen (30 per cent) of these children are under one year of age, and 503 are between the ages of one and seventeen years. They were all residents of the City and County of Honolulu (Oahu), Hawaii.

The age distribution of a study group is important, because the incidence rate in children does not increase in direct proportion to their age, since the peak of the onset age of asthma, for instance, is at two to three years (Table III). The age distribution of a group (Table IV), therefore, must be considered when comparing data from different sources. The

Honolulu group is fairly typical of the average pediatric practice according to a survey of sixty pediatricians in the state of Washington.[12]

Only two general pediatric population incidence studies on the mainland are available to compare with the Honolulu data. One is that of Crook *et al*[10] from Jackson, Tennessee. These data (Table V) were obtained in

TABLE V. INCIDENCE OF ALLERGIC DISEASES IN A PEDIATRIC PRACTICE IN HONOLULU
Comparison of Studies

	Myers (Hawaii)		Crook et al (Tennessee)		London (North Carolina)	
Number Studied	718		1225		1500	
Diagnosis	Cases	Rate*	Cases	Rate*	Cases	Rate*
Allergic	216	30.0	175	14.0	99	6.6
Probably allergic	82	11.0	220	18.0	0	0
Non-allergic	420	58.5	545	45.0	1401	93.4
Unknown	0	0	285	23.0	0	0
Asthmatic	111	15.4	58	4.7	35	2.3
Probably asthmatic	23	3.2	8	0.6	0	0
Perennial allergic rhinitis	92	12.8	70	5.7	?	?
Seasonal allergic rhinitis**	?	?	27	2.2	3	0.2
Urticaria	48	6.7	8	0.6	12	0.8
"Eczema"†	84	11.7	60	4.9	45	3.0
"Eczema" and asthma	41	5.7	13	1.0	?	?
Multiple allergies	112	15.6	135	11.1	?	?

*Cases per 100 of sample population
**Pollinosis
†"Eczema" here means atopic dermatitis or "infantile eczema"

1954 from 1,225 patients visiting the office on sixty equally spaced study dates. "Conservative diagnosis" of allergic diseases from examination, laboratory data, and history was classified under four groups: (1) allergic, 14 per cent; (2) probably allergic, 18 per cent; (3) non-allergic, 45 per cent; and (4) unknown, 23 per cent. There are some differences in the methods of obtaining data and in the age distribution, but I do not believe that these are of much significance in this instance. The importance of the racial differences is not known. Crook's series was composed for the most part of sick children (85 per cent); approximately 15 per cent were well-baby checkups; and approximately 20 per cent were under one year of age as compared with 30 per cent in the Honolulu group. Some of the data were obtained from the parents since the children had not all been followed since birth.

London[9] in 1937 in North Carolina found thirty-five cases (2.3 per cent) of asthma out of the first 1,500 patients seen by him in his pediatric practice. This same rate was found again in 1951.[8] These were cases diagnosed as asthma one or more times while under his care. The actual rate in these children was probably higher than 2.3 per cent because they also were not all followed continuously from birth to date of study.

Most other detailed surveys were done by allergists on groups of allergic children. These data, therefore, gave the distribution rates of the various allergies and associated conditions in allergic children (Table VI). The

Honolulu rates for allergic children are similar to those found by Crook,[10] Glaser,[13] Clein,[14] and Ratner,[15] if the differences of the age distribution of the groups and methods of collecting and grouping data are considered. These data are not the incidence rates in a normal population and should not be confused with those in Table V. Glaser's adult group is included to show the effect of age on the rates, as compared with the pediatric age groups.

TABLE VI. DISTRIBUTION OF ALLERGIC AND ASSOCIATED DISEASES IN ALLERGIC CHILDREN

	Myers (Honolulu)		Crook (Tennessee)	Glaser (New York)	Clein (Washington)	Ratner (New York)	Glaser (New York)
Allergic Cases	216		175	516	100	250	200*
	Cases	Rate**	Rate**	Rate**	Rate**	Rate**	Rate**
Asthma	111	51.0	33.0	53.0	26.0	63.0	41.0
Perennial allergic rhinitis	90	42.0	40.0	28.0	59.0	?	35.0
Seasonal allergic rhinitis†	0	0.0	15.0	33.0	38.0	10.0	41.0
Urticaria	35	16.0	4.5	16.0	12.0	10.0	35.0
"Eczema"††	84	39.0	34.0	38.0	33.0	44.0	1.0
Eczema, only	20	9.0	6.0	6.5	?	?	?
Eczema and asthma	38	17.0	22.0	17.0	?	?	?
Multiple allergies	112	52.0	77.0	79.0	?	?	?

*Adults
**Diagnosis per 100 allergic cases in study group
†Pollinosis
††Atopic dermatitis or "infantile eczema"

The perennial allergic rhinitis rate in the Honolulu group is probably less than it should be, because it is a common chronic condition in Honolulu children and may be relatively mild and so constant that the symptoms are often ignored by the patient's parents, and the physician. This would also reduce the rate in the multiple allergies group. "Seasonal" allergic rhinitis or pollinosis cases in Hawaii are difficult to diagnose accurately, as noted above. They probably are represented by periodic exacerbations of the perennial allergic symptoms.

Since the incidence rate of allergic diseases was apparently higher in Honolulu than on the mainland, other comparisons were studied in the hope of finding some explanation for the unusually high rate. One of the main differences in the Honolulu group was its racial composition (Table VII).

In Table VII the number of cases of allergic diseases recorded for each race, their percentage of the total population and the per cent that they represent of their racial group in the study are calculated. The Japanese have the highest rate of allergic children and the highest rate for each allergic disease, especially eczema. The mixed racial group of children are second and Caucasians are third. Hawaiians have a higher rate of allergies in this study, but their total number is too small to be reliable. The asthma rate, however, is about the same in each group.

It will be noted that the total population classified in racial groups is less than the total of Table VI. This is because there were 210 infants under

one year of age who had no allergies when recorded and were not classified according to race or sex.

It would seem that the high incidence rate of asthma in Honolulu is not found in any one racial group, although the Japanese and the "mixed race" group have a higher "allergic" rate than the Caucasians.

TABLE VII. ALLERGIC DISEASE DISTRIBUTION IN VARIOUS RACIAL GROUPS IN A HONOLULU PEDIATRIC PRACTICE

Racial Stock	Total		Allergic		Asthma		"Eczema"*		Allergic Rhinitis		Hives	
	Pop.	All Cases (Per Cent)	Cases	Rate**	Cases	Rate**	Cases	Rate**	Cases	Rate**	Cases	Rate**
Caucasian	216	42.0	75	35.0	43	20.0	24	11.0	26	12.0	15	7.0
Japanese	206	40.0	96	47.0	46	22.0	45	22.0	38	18.0	25	12.0
Mixed races†	50	10.0	21	42.0	10	20.0	9	18.0	5	10.0	5	10.0
Chinese	16	3.0	4	25.0	2	12.0	2	12.0	2	12.0	1	6.0
Korean	12	2.0	3	25.0	1	8.0	1	8.0	1	8.0	0	0
Filipino	11	2.0	3	27.0	2	18.0	1	9.0	2	18.0	0	0
Hawaiian	6	1.0	3	50.0	2	33.0	1	16.0	0	0	0	0
Total	517	—	205	40.0	106	20.0	83	16.0	74	14.0	46	9.0

*Includes allergic or atopic dermatitis and infantile eczema
**Cases per 100 per cent of racial group
†Includes all children with parents of different races

It has been assumed by many allergists that, as Vaughan[16] concludes after reviewing the literature, "The incidence of allergy among Caucasians appears to be actually higher than among other races." However, these data would seem to bear out the statement of Urbach and Gottlieb,[17] that "in principle, all races can become allergized, if exposed to sufficient stress and a suitable environment." Hara[18] found that Japanese in Southern California had an incidence rate of 3.5 per cent of hayfever, although there is practically no hayfever in Japan or Korea. He noted that they lost their hayfever symptoms when they returned to Japan. He also states that "asthma is prevalent in Japan and in Japanese living in Southern California."

Respiratory infections are, of course, an important cause of bronchial asthma. We have no respiratory infection rate data to compare with the mainland except for a U. S. National Health Survey[4,5] conducted for twelve months in 1958-1959, which states that: "The incidence of acute upper respiratory conditions is higher on Oahu (City and County of Honolulu), Hawaii, than on the mainland (Table VIII). The difference is not entirely due to the higher proportion of children in Hawaii, because it existed in each age group except sixty-five and older. The general pattern of distribution of acute illnesses by type, age, and sex is the same as on the mainland. [The "acute respiratory conditions" above probably include both infections and some allergic diseases. The proportion of each is not known.] However, chronic sinusitis prevalence rates are lower, and chronic bronchitis rates are about the same as on the mainland[5]."

TABLE VIII. ANNUAL INCIDENCE OF "ACUTE"* RESPIRATORY CONDITIONS
U. S. National Health Survey 1958-1959

Conditions	All Ages		Under 5 Years		5-14 Years	
	U.S.	Hawaii	U.S.	Hawaii	U.S.	Hawaii
Upper respiratory rate**	83.1	112.1	157.5	241.7	114.9	124.2
Other respiratory rate**	42.6	50.8	53.6	46.5	60.6	61.2

* Any condition lasting less than two weeks
** Attacks per 100 persons interviewed

DISCUSSION

In an article entitled, "Development and Course of Asthma in Children," Susan Dees,[8] says in her conclusion: "Incomplete as our information is at present, it is obvious that asthma kills five times as many people as polio, for example, and undoubtedly incapacitates as many if not more. One of the great advances in the understanding and control of this great health problem could come from accurate statistics on its incidence and progress."

Hawaii offers a unique opportunity for the clinical study of allergic diseases, especially bronchial asthma and allergic rhinitis. In the first place, the incidence rate is apparently much higher than on the mainland. The clinical study of asthma, for instance, is complicated by the possibility of many different etiologic factors operating at the same time. Hawaii has the advantage of having fewer "natural" factors. It has an "ideal" climate most of the time, minimum temperature and barometric pressure fluctuations, low pollen and mold spore counts, and no ragweed. "Clean" sea air is a relatively stable factor, due to trade winds that are fairly constant in direction and velocity for several weeks or months at a time. Kona winds from the opposite direction do occasionally prevail for a few days or weeks at a time. Localized areas of high (150 inches per year) and low (10 inches per year) rainfall are located within a few miles of each other. The average rainfall for Honolulu is 25 inches per year. House dust control is much easier here because of open, airy, homes and, in many localities, there is no necessity for central heating or wool rugs or blankets.

The "relative humidity" is not high for a tropical climate. The relative humidity daily average for Honolulu[3] is 75 degrees in the A.M. and 64 degrees in the P.M., for instance, and the comparative figures for Western Tennessee are 80 degrees in the A.M. and 70 degrees in the P.M.

Acute upper respiratory infections may be higher than on the Mainland.[5] Since there is a relatively captive population living on several different islands, the epidemiology of infections could be more easily followed, and their relationship to the asthma attack rate studied. A stable population of several different races with different cultural and dietary habits also add interest and research possibilities.

Under these circumstances, many clinical research projects associated with allergies would seem to be indicated, such as:

1. Comprehensive pollen and mold and rust spore count surveys.

2. Investigation of other air contaminants, soil, dredged coral, insects, and so forth.

3. Investigation of possible etiologic factors in "clean" ocean air (ionization,[19] NaCl, and so on).

4. Skin testing on a large scale using local pollens, molds, and rusts.

5. Investigation of possible racial factors, diets, and so forth.

6. Study of the relative antigenicity of local house dust, as compared with mainland house dust.[20]

7. Detailed study of weather factors.[21]

8. Correlated studies on several islands as to asthma incidence rates, and related factors such as weather and infections.

9. A cooperative clinical study of the etiology of asthma in children in Honolulu.

10. More detailed statistical study of the "asthma-hayfever and acute respiratory conditions," data collected by the U. S. National Health Survey, 1959-1960.[4]

CONCLUSION

1. The incidence rate of some allergic diseases in children is probably higher in Honolulu than on the mainland.

2. The incidence rate of asthma in children is three or more times the rate in comparable studies on the mainland.

3. The Japanese and "mixed races" in Honolulu have a higher total incidence rate of allergic diseases than the Caucasians. However, the asthma rate is about the same.

4. For many reasons discussed above, it is believed that Hawaii offers a unique opportunity for the clinical investigation of certain etiologic factors of allergic disease.

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Straub Clinic
1000 Ward Avenue

THE NATURE AND SYMPTOMS OF HAY FEVER

So long as the supply of pollen is kept up, the sneezing and discharge of serum continue; but the frequency and severity of these do not in all stages of the disease entirely depend upon the quantity of pollen inhaled. The degree of occlusion in the nasal passages varies in the day as well as in the night, but not to the same extent. If the occlusion has been tolerably complete in one or both nostrils for some hours, and by any chance suddenly lessens, the patient may for the reasons I have just adduced have a violent attack of sneezing, notwithstanding that he may be inhaling a very small quantity of pollen at the time. If the average quantity is large, however, the swelling of the submucous tissue continues—subject to the variations above alluded to—and the alae nasi, as well as the lining membrane of the nares, become tender and inflamed, and have a tendency to bleed slightly if rubbed. Under these circumstances the patient frequently finds that air can only be drawn through the oral aperture, and if he sleeps he finds on awaking that the tongue and the whole buccal cavity are more or less parched. As the disorder progresses the discharge from the nostrils becomes more inspissated and puriform, especially early in the morning.—C. H. Blackley, M.D., from *Hay Fever: Its Causes, Treatment, and Effective Prevention,* Bailliere, Tindall and Cox, London, England, 1880.

INVESTIGATION OF ATOPIC DERMATITIS IN CHILDREN WITH SPECIAL REFERENCE TO MOLD ALLERGY

ALBERT ZUCKER, M.D., F.A.C.A.
New York, N.Y.

REVIEW OF PERTINENT LITERATURE

ATOPIC DERMATITIS is recognized as being "one of the most complicated and obscure situations in all medicine,"[1] and its allergic etiology is still being challenged.[2] Milder[3] states that "the allergic sensitivity is of little etiological importance." Statistical evaluations of allergens claimed to be responsible for this condition show great variations. Glaser[4] and Clein,[5] among others, believe cows' milk allergy to be one of the chief causes of atopic eczema in infants and children, and describe excellent results with milk substitutes. Ratner, Crawford and Flynn[6] conclude that "milk, which in the past was considered one of the prominent sensitizers, appears of less importance in our series." They believe that multiple sensitivities must be considered. Sherman and Kessler[7] are of the opinion that infantile eczema in its early stages is related to sensitivity to cows' milk, orange juice or fish liver oils, but when the dermatitis persists, additional etiologic factors are apparently involved. Climatic influences,[8] high altitudes,[3,9] the sweat retention syndrome,[10] abnormalities in sweat electrolytes[11] and irritating or sensitizing contacts[12,13] have been connected with atopic dermatitis. The psychosomatic aspects have been emphasized by Stern,[14] Cormia[15] and numerous other authors.

Collins-Williams and Ratner[16] state that "every year there are new papers out stressing the importance of inhalants in the etiology of atopic dermatitis and stressing the value of hyposensitization." Tuft[17] found fifteen marked reactors to house dust in fifty-four cases and reports improvement after house dust desensitization, and aggravation when exposed to dust.[18] He calls house dust one of the most important allergens in atopic dermatitis.[19] The exact nature of the atopen is still unknown, and according to Boyd[20] the current prevailing opinion is that it results from disintegration of cellulose, particularly cotton and kapok. Frior and Tesco[21] suggested that fungi might produce breakdown products from materials contained in house dust. Harris and Shure[22] state, "it is tenable that the common reaction to house dust is due to air-borne spores in its composition." Tuft *et al*,[17,18,23-26] Jillson *et al*,[27,28] and Diamond[29,30] are impressed with inhalant allergy as an important factor in atopic dermatitis and cite the frequency of positive reactions to house dust and mold extracts. The good results obtained with

From the Allergy Department of Knickerbocker Hospital and the Children's Allergy Clinic of Harlem Hospital, New York City.
Albert Zucker, M.D., is Associate Visiting Pediatrician, Allergy Clinic Harlem Hospital, New York City.

hyposensitization with these allergens are stressed by these authors. Some of the investigators suggest that much higher dilutions of mold extracts should be used in the treatment of atopic dermatitis.

Research in atopic dermatitis has frequently been confined to testing and treating those patients with a single or only a few mold extracts, depending apparently on cross reactions with other molds. According to Prince and Morrow,[31] "Alternaria is not a universal dematiaceous allergen and universal cross immunity cannot be anticipated among all the molds. Therefore treatment mixtures should be made as polyvalent as possible." Van Der Werff[32] is of the same opinion and feels that fungus allergy of generic nature alone cannot yet be regarded as a general rule with any certainty. Careful study of house dust for molds by Schaffer, Seidmon and Bruskin[33] showed twelve fungi to be most frequently found in dust samples in their locality in New Jersey. They discovered that thirty-six of the fifty organisms present in the air were also in house dust samples. They feel that, with few exceptions, the fungi which are most constant in appearance in the air are most important from the clinical standpoint. Viable spores are present in house dust throughout the year. Certain peaks caused by vegetational and climatic changes are observed, with marked drops in atmosphere counts occuring in winter, especially when the ground is snow-covered.

A routine allergy workup, a thorough study of the mycological environment and skin testing with a variety of fungus extracts might be helpful in coming a step closer to the solution of this puzzling disease.

MATERIAL AND METHODS OF INVESTIGATION

A study of twelve Negro children with atopic dermatitis was started in June, 1957. All patients were referred by the Pediatric or Dermatological Departments, where some of them had been treated. The material is therefore far from unselected, since an unknown number of children who had responded to elimination diets or symptomatic treatment was not referred to the allergy clinic.

All parents were instructed to abstain from local or systemic treatment and to continue their children on a regular diet. A thorough history was taken at the first interview. The seven male and five female patients were between the ages of six months and eleven years, the average age being slightly above four years. Eight children had asthma as a secondary disorder. The average onset of eczema was slightly below one year of age, of asthma, about two years. Ten children had aggravation of their skin lesions in summer, and two were worse in winter. Parents or siblings of nine children were afflicted with a major allergy. Five patients had prominent manifestations of gastro-intestinal disturbances (vomiting, diarrhea or colic) during infancy. Food elimination had been previously tried in ten children at other clinics without any obvious benefit. Complete laboratory and physical examinations were done on all patients.

The children were skin-tested by the punch method with a total of 134 extracts of foods and inhalants, including ten fungus extracts. Thereafter routine intradermal tests were done. Finally, all patients were tested with twenty fungus species using two different types of extracts.* Moderate or marked reactions to common allergens were as follows:

Inhalants—house dust, eight; horse epithelium, three; mixed ragweed, three; dog epithelium, two; feathers, one; wool, one; grasses, one; and trees, one.
Foods—cereals, three; egg, two; and milk, one.

Reactions to foods were recorded, but intentionally disregarded. Eleven out of this group of twelve children showed at least one moderate reaction to the fungus extracts, and one patient had only three mild reactions. Table I indicates the fungus species used for testing and the frequency of immediate wheal reactions, arranged according to the total reactions observed for each species.

TABLE I. FUNGUS SPECIES USED FOR TESTING

Fungus Species	Immediate Reactions			Total Reactions
	Mild	Moderate	Marked	
1. Alternaria ten.	6	4	1	11
2. Fusarium	5	3	—	8
3. Stemphylium	2	3	1	6
4. Curvularia	4	1	1	6
5. Phoma	3	1	1	5
6. Spondylocladium	4	—	1	5
7. Rhizopus	3	2	—	5
8. Hormodendrum	3	2	—	5
9. Helminthosporium	5	—	—	5
10. Rhodotorula	1	3	—	4
11. Chaetomium	2	2	—	4
12. Botrytis	2	2	—	4
13. Aspergillus fum.	1	2	—	3
14. Penicillium	2	1	—	3
15. Mucor	—	1	1	2
16. Saccharomyces	1	1	—	2
17. Aspergillus nig.	1	1	—	2
18. Monilia sit.	—	1	—	1
19. Trichoderma	1	—	—	1
20. Pullularia	—	—	—	—

Starting in June, 1957, and for two years thereafter, a total of seventy-nine petri dishes with Glucose Sabouraud medium were exposed on the roofs and high window ledges of the two hospitals which are located in the same area where these children were living. The species found are listed below according to the number of petri dishes on which they were identified (not colony counts).

Penicillium	38
Hormodendrum	31
Pullularia	27
Alternaria	22
Aspergillus	17
Monilia Sit.	8
Mucor	8
Streptomyces	4

*Hollister-Stier Laboratories (Type 33 Molds) and Center Laboratories.

Also identified were: Rhizopus, Sepedonium, Stemphylium, Helminthosporium, Gliocladium, Macrosporium, Trichoderma, Cephalosporium, Paecilomyces. Yeast and unknowns were found on many extramural and intramural cultures, and are not listed.

In order to investigate the mycological environment of these patients, sixty-two petri dishes with the same medium were exposed for approximately ten to twelve minutes in the patients' homes. These children were all living in low rental tenement houses under poor economic conditions. Most families were recipients of welfare aid. The parents frequently complained that their homes were damp and poorly ventilated. The indoor molds are listed in the same manner as the outdoor molds and were identified as follows:

Penicillium	30
Hormodendrum	15
Aspergillus	10
Pullularia	8
Alternaria	7
Rhizopus	6
Mucor	6
Monilia Sit.	4

Also identified were: Gliocladium, Phoma, Streptomyces, Paecilomyces and Scopulariopsis.

The correlation between fungi found on indoor cultures and the patients' skin reactivity was excellent in three children, good in five and poor in four.

TREATMENT

A mixture of fungus extracts to which the children showed definite reactions was injected at weekly intervals, starting with a 1:1,000,000 dilution of the "Type No. 33" extracts or 1 PNU/cc of the regular extracts. The doses were gradually and carefully increased until a concentration of 1:10,000 or 100 PNU/cc was reached. One patient showed aggravation of the eczema with itching on several occasions on the day following the injection. When the increase was made in smaller increments, however, this reaction failed to appear. Two patients with severe seasonal rhinitis and asthma received ragweed extracts. The eight house dust reactors were started on a 1:1000 dilution of commercial house dust extract, and doses were gradually increased as tolerated. No elimination diets were used.

RESULTS

The eczema of ten patients cleared completely after an average treatment time of about seven months. Two patients were greatly improved. This group was treated and observed for about two years. The effect on the eight children having concomitant asthma was good: four patients have been entirely free of asthma, three patients had only mild and rare attacks and one patient had one severe attack following an upper respiratory in-

fection. The average eosinophile count, which was about 9 per cent prior to treatment, had dropped to about 3 per cent after treatment.

COMMENT

The small number of patients (twelve) studied was insufficient for statistical evaluation, and discrepancies with other series are to be expected. These children represent an unknown percentage of all cases of atopic eczema seen at the two hospitals. Most of them had failed to respond to routine treatment at other clinics. As I had stated previously, they cannot be considered a typical group of eczema patients. Atopic eczema, it must be remembered, is a self-limited disease with some spontaneous remissions. The occurence of the "dermal-respiratory syndrome" in two-thirds of these children is higher than reported in the literature.[34] The drop of the average eosinophile count in this group certainly suggests an amelioration of the allergic state.

The role of mold and house dust hyposensitization in this group is difficult to evaluate. Baer[35] states, "All the evidence available at present is against a single etiologic mechanism and favors a multiplicity of contributory factors which superimpose themselves on a peculiar terrain." These two allergens might well be contributory or trigger mechanisms. The aggravation of atopic eczema in summer and the improvement in winter, in dry localities and at high altitudes may well be caused by contributory climatic factors. However, the higher atmospheric mold spore content during the damp summer months and the considerably lower spore content in winter, in dry climates or at high altitudes could also explain climatic or geographic influence upon this disease, if mold allergy is a factor of importance. Reactions to multiple fungus extracts have been observed when larger numbers of extracts were used. Schaffer and Seidmon[36] tested with thirty-five species and found numerous reactions to fungi in eczema patients. The question is, then, whether or not these skin reactions were evidence of clinical sensitivities in these twelve patients. Passive transfer tests, inhalation tests or immunological methods might also be used to clarify the role of fungi and house dust. Intramural and extramural fungus cultures showed only slight differences in this locality, as could be expected, because all indoor molds gain access into the homes from the outside and are in constant communication. There was some correlation between intramural fungi and skin reactivity.

Numerous children were treated in private practice with mold extracts and showed gratifying results. According to this study, mold allergy might be a factor in the difficult problem of atopic eczema. The author is continuing this investigation and feels that further work in this field with a larger number of unselected patients using a double blind method might solve this problem.

SUMMARY AND CONCLUSION

In order to detect a relationship between mold allergy and atopic eczema, twelve children afflicted with atopic eczema were investigated. After thorough testing which included twenty fungus species, and after investigation of the mycological environment, these patients were treated with house dust and mold extracts. The results in these twelve children, as well as in eight of the children with concomitant asthma, were excellent.

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315 East 167th Street

THE QUALITIES OF SCIENCE AND OF THE SCIENTIST

The spirit of science then is, first of all, the wish to know, the urge to seek, the desire to comprehend the universe.

Secondly, the spirit of science is the spirit of courage. The scientist is not bound by ancient tradition. Copernicus dared to cast aside the Ptolemaic theory though it had dominated man's thought for centuries. Vesalius challenged the authority of Galen's anatomy even though it had ruled since the time of the Romans. Scientists did not fear Newton's "Principia," because it was new. They did not flee from Maxwell's electromagnetic theory of light because it was revolutionary. Twentieth century scientists have not rejected Planck and Rutherford and Schrodinger and Einstein because their ideas were new. On the contrary, they have rejoiced in each new discovery.

Third, science is the spirit of tolerance. The scientist knows that there is no monopoly upon truth. He sees the advance of science as a great cooperative venture of all nations and peoples down through the years. The roll of every science is an international one. Copernicus was a Pole, Tycho, a Dane, Kepler, a German, Galileo, an Italian, Newton, an Englishman. The story is the same today. The theory of Einstein receives its chief verifications at the hands of English and American scientists.

The scientist is tolerant of other men's points of view. Realizing how frequently he must change his own views in the face of new evidence, he is never scornful of the other man's point of view. He realizes how little mankind knows and how much is yet to be learned and the realization makes him tolerant.

And finally, the scientist is humane. He is concerned for the future of mankind. The picture of the scientist as a man who shuts himself away in his laboratory like a hermit in a cave is an unfair picture. There are, of course, such individuals, but they are not representative of science.—David Dietz—*The Story of Science,* The New Home Library, New York, 1942, by arrangement with Dodd, Mead & Company

HEARING DISTURBANCES IN ALLERGIC CHILDREN

VICTOR L. SZANTON, M.D., F.A.C.A.
WILLETTE C. SZANTON, M.A.
Derby, Connecticut

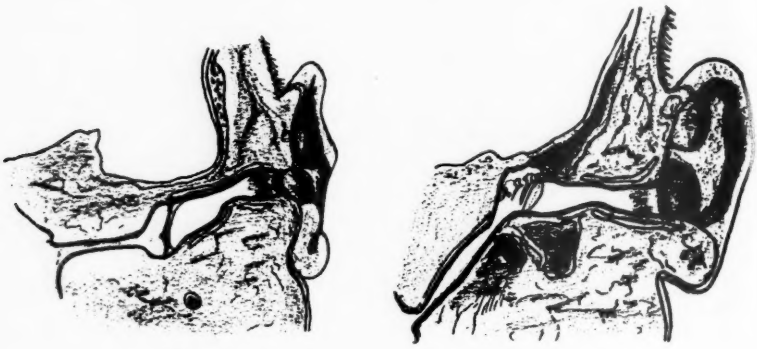
A SCHOOL hearing test in March showed that David T., age seven, had a moderate degree of deafness. Noting that he had a "cold" at the time of testing, however, the school nurse discounted the results, and scheduled him for retest. Pupil loads being what they are, David's retest came the following March. Results, and health picture, were much the same as before. The otologist who saw him on referral two months later found scarcely any disturbance of hearing, and advised Mrs. T. to "wait and see." In the last week of September of the same year, David's hearing, retested, was demonstrably superior. This should have closed the case, proving once more, as so often claimed, that hearing tests on young children are notoriously unreliable. One more test was performed, however, just ten days later. Suddenly, a degree of loss similar to that demonstrated the previous March was back with David again. By which test should the confused family and school be guided?

It is one of the purposes of this presentation to demonstrate that although these results seem to be mutually contradictory, they are, in fact, all accurate and reliable measurements of function in a boy *who varies,* with variations in his environment. Cutaneous testing confirmed the clinical history; David was sensitive to house dust. Symptomatically and by cutaneous testing, he was not sensitive to ragweed. On October 3, between the test showing excellent hearing, and that again showing a hearing loss, the hot air heat had been turned on in David's home.

In 1958, Wishik, Kram and Koch[1] citing their eight-year study of school children in Reading, Pennsylvania, reported hearing tests on 1,726 children. They stressed the frequency of short duration hearing loss and suggested that the usual biennial interval for school hearing surveys is too long. Although these authors were concerned with factors other than etiology, and did not relate their findings either to seasons of heightened allergenic stress, or to otologic symptoms, note was made of histories indicating "the frequent existence of nasopharyngeal infection." They recommended that hearing tests be given to any child "when infections or allergic involvement of ear, nose or throat are frequent or excessive." A seemingly unrelated finding of this excellent and many faceted study is that among children five to seven years of age, who "failed their first audiometric tests, 48.4 per cent failed later tests." The unstated corollary of this observation is that 51.6 per cent of these children overcame or outgrew their hearing disturbance within the eight years of follow-up covered by the report. We are, therefore, presented with two phenomena not customarily recognized in

discussions of hearing loss: (1) the intermittent hearing loss of varying intensity and duration, and (2) the hearing loss which disappears as the child grows older.

It is time for an integration of those findings made in the fields of otology, audiology, and allergy, which, when taken together, will simultaneously explain these phenomena and give new significance to the findings themselves.



(A) (B)

Fig. 1. Oblique sections to show the direction of the external auditory meatus and of the eustachian tube (A) at birth, and (B) in the adult. Part A is approximately life-size; Part B is reduced to the same size for comparison.

Of first importance is a brief review of the anatomy and physiology of the eustachian tube, best described by Wilson[2] (Fig. 1, A and B). "The eustachian tube is different in infants as compared to adults. In the former (infants), the tube is very much shorter, being less than half the adult length (14 mm. compared to about 35 mm.), while the tympanic orifice and the calibre of the tube are quite as large as in the adult. The tube as a whole, therefore, is relatively much wider than in the adult. The osseous and cartilagenous portions of the tube are very much in the same straight line, whereas in the adult they form an obtuse angle at the junction. The direction of the tube is almost horizontal, the tympanic orifice being practically at the same level as the pharyngeal opening, while in the adult it is 15 mm. higher. The pharyngeal opening of the tube at birth is opposite the edge of the hard palate, while in the adult it is at least 10 mm. above this level."

The eustachian tube is a combined ventilating and drainage channel. It is normally closed, and opens periodically to ventilate the tympanic cavity. Its chief function is to maintain an equal air pressure on each side of the tympanic membrane, i.e. in the external and the middle ear. "This is essential to a free-swinging lever system, as a marked difference in pressure between the outer canal and the tympanic cavity tends to lessen

the effectiveness of sound vibrations upon the ossicles. The manner in which this air pressure equalization is effected is through the intermittent openings of the muscular portion of the tube which take place simultaneously with the act of swallowing."[3]

The mechanism and effects of eustachian tube dysfunction should next be noted. Birrell[4] points out that the result of obstruction of the eustachian tube is that oxygen is absorbed in the middle ear, and negative pressure develops because the air thus lost cannot be replaced until the tube opens. Since air in the external meatus remains at atmospheric pressure, the tympanic membrane becomes indrawn. This differential loading of the two sides of the membrane results in a conductive deafness, which is called vacuum otitis. The main symptom is hearing loss, usually unassociated with any pain. Following this, exudation of seromucus into the tympanic cavity occurs. The outstanding symptom is then a sensation of fullness in the ear, with transitory tinnitus and hearing loss. This condition is called secretory or serous otitis media, and is a disease entity commonly met with in otologic practice. Revealingly, Armstrong[5] states that in his series of 1,016 ears with fluid, 78 per cent occur in children eight years of age or under. Davison[6] reports that over 65 per cent of middle ear effusions occur under ten years of age and another 16 per cent in the eleven to twenty-year age group.

The commonest cause of obstruction of the eustachian tube is an increase of lymphoid tissue in the nasopharynx. The etiology of this hypertrophy being seldom discussed, removal of excessive tissue by surgery or irradiation has been the customary procedure without consideration of causes that may stimulate its regrowth. The matter of etiology has recently been receiving increased attention, however. Clein[7] has reported a recurrence of lymphadenoid tissue in the tonsillar fossa in 27 per cent of allergic children as compared with 3 per cent of non-allergic children. Glaser[8] has the impression that any child who has to have tonsils or adenoids or both removed more than once is an allergic child. Solow[9] states that one-third of all serous otitis cases which he has investigated are due to allergy, and further that one of the main symptoms of allergic otitis media is a fluctuating hearing loss.

Kuhn[10] has emphasized the need to search out hearing disorders due to allergy. He stated, as did Solow after him, that the best clue is the variability in the presence and intensity of hearing changes from day to day. He suggested the diagnosis be made from the patient's history, the variability of symptoms over a time, and a base line audiogram followed by a test dose of epinephrine and a repeat audiogram. If the test is positive, i.e., showing subjective changes and an increase in hearing acuity, the patient should be investigated thoroughly from the allergic standpoint.

Canfield[11] points out that not only infection but allergic reaction of the nose, throat *and ears* can cause a hearing loss. This refers to an understanding that the mucous membrane of the eustachian tube is identical in

structure and in function with the mucous membrane of the nasopharynx of which it is an extension.

Derlacki[12] writes: "Allergic involvement of the middle ear is a part of the generalized allergic reaction of respiratory epithelium with selective emphasis upon the mucous membranes of the eustachian tube of the tympanic cavity." It would, therefore, appear that in considering allergy of the mucous membranes of the upper respiratory tract, one should include not only the nasopharynx and the paranasal sinuses but also the eustachian tubes and the mucosa of the tympanic cavity. Dohlman was the first investigator to find eosinophilia of the serous fluid in otitis and devised the theory that sensitization is induced by a foreign protein—especially cow's milk, the milk being forced up into the middle ear in the usual bottle feeding of babies. The anatomic configuration of the eustachian tube in the infant and young child, differing as it does from that of the adult, enhances the chance for this type of sensitization. In addition, the infant and young individual spends many more hours than the older person in a supine position. Visualizing this in relation to position, width, and straightness of the immature eustachian tubes, we recognize the decrease in tube drainage and the increased opportunity for collection of nasopharyngeal secretions in and about the tubal orifice.

Let us recognize then that an interaction exists between the allergic reactivity of the total upper respiratory mucosa (with the well-known fluctuations of severity linked to seasonal and environmental factors), and the developmental dynamics of eustachian tube growth, function, and dysfunction. There are variables on both sides of this interaction, but they are predictable variables, and the mode and effects of their interaction are predictable. We are thus better able to understand the frequently noninfectious origins of serous otitis media, and of vacuum otitis with its concurrent, often intermittent hearing loss which tends to disappear as the child grows towards adolescence.

As we have noted, otological literature is replete with reports on the incidence of conductive hearing loss and, though to a lesser degree, we also find allergists reporting on the incidence of allergy as one causative factor in such loss. Case loads in each instance, however, have derived from otologic referrals and are composed entirely of patients who have a demonstrated hearing loss.

With a converse approach to the problem, the investigation here being reported was projected to discover the percentage of hearing loss in a case load composed entirely of allergic patients. These were drawn from the Pediatric Allergy Out-Patient Department clinic at the Hospital of St. Raphael in New Haven, Connecticut, and from the private practice of the authors. All were individuals with allergic rhinitis—perennial or seasonal, or asthma, or eczema, or combinations of these syndromes. Allergy was diagnosed on the basis of positive family history, clinical history and findings, nasal smears, and confirmation by positive cutaneous reactions to

scratch or intradermal tests or both. The study was limited to 100 individuals. Of these fifty-five were male, forty-five female. Fifty-nine of the patients were under nine years of age; forty-one were nine years old and over. Eighteen per cent of the patients had no upper respiratory symptoms, suffering from other major allergies previously mentioned.

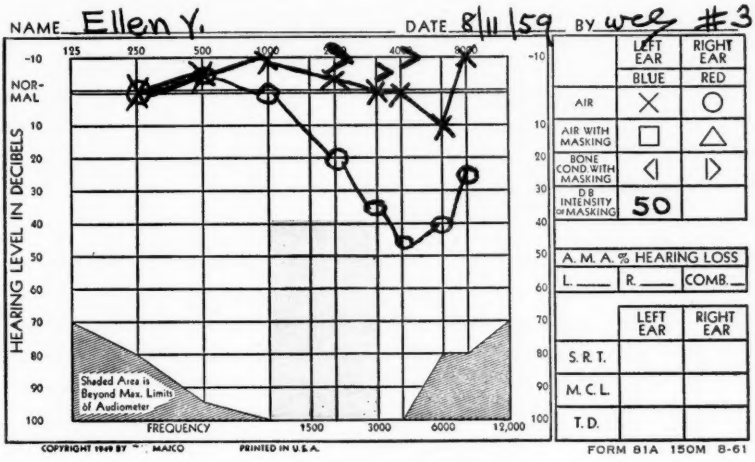


Fig. 2. Audiogram record.

Concurrently with diagnostic procedures, and before therapy was instituted, each patient participated in a series of three audiometric tests given at intervals ranging from one week to one month apart. There was only chance correlation between test dates and individual periods of heightened allergic distress. Prior to testing, it was ascertained that patients' ear canals were free of cerumen and that no infection was present. Patients were enjoined from using any antihistamine or nasal decongestant for a minimum period of 36 hours before each test. The only exception to this injunction was made when antihistamines were specifically prescribed to assist with a differential diagnosis. In these instances, and when periods of conditioning were necessary with the youngest patients, more than three hearing tests were given. It is with the results of these audiometric series, and their interpretation in the light of the previous considerations, that this paper is principally concerned.

An audiogram is a standardized form, upon which are recorded findings relative to the way in which a specific individual hears a standardized set of sounds. These tones are identified by their vibratory frequency in cycle-per-second notations, and are presented in octave or semi-octave steps; changes of intensity are measured in decibels, and are customarily made in five-decibel steps. An audiometer produces the test tones which may be presented to either ear by way of air or bone conduction, and methods

both of presentation and of annotation on the audiogram have been standardized. (Fig. 2)

The report form is designed to relate findings to an established norm for hearing acuity, here indicated by the line marked zero. As with other clinical measurements, however, such as those for body temperature, blood pressure, pulse and respirations, this norm is actually considered as a reference point for normal function. Judgment and experience accept individual variations up to plus or minus 10 decibels around this point, as falling within normal limits. Additionally, in recognition of the masking effects of environmental noise upon the hearing of an individual being tested, most hearing surveys include a consideration of the noise conditions of the specific testing site, and the limits of normalcy for that survey are extended accordingly.

The present study is concerned with findings based on a total of 396 audiograms which trace the hearing patterns of 100 allergic patients. The tests were conducted in an isolated, sound-treated cubicle. In those few instances where this was not possible, limits of normalcy for frequencies customarily affected by variations in ambient noise, were adjusted. All the tests made on any one patient were conducted in identical surroundings. All tests, on all patients, were made with the same calibration-checked audiometer. All testing was performed by the same individual. Hearing loss, as considered from this point on, will indicate minimum findings of a drop of acuity of at least 15 decibels in at least two test frequencies in one ear. In actuality, only two of the loss cases reported in this study demonstrated this minimum finding. All other patients had more marked loss.

Bone conduction tests were performed as seemed necessary, and all cases under discussion here reflect a disorder of the individual's sound conduction system. Patients ranged from three and one-half years of age upwards, and with many of the younger ones several periods of orientation and conditioning activities had to precede actual audiometry, so that the child would be ready to listen and to respond reliably.

As testing progressed, it became increasingly apparent that some patients maintained excellent hearing acuity while suffering a high degree of upper respiratory congestion. Severity of allergic symptoms, which were frequently accompanied by a disturbance of acuity in the younger child, were seldom so reflected in the hearing of the older or physically more mature patient. Recalling the findings of Armstrong and Davison relative to age factors in the incidence of secretory otitis media, and aware of the Rapaport, Szanton, Appel[13] survey which demonstrated the spurt in onset of incidence of allergic syndromes between ages four and nine, it was decided to study the results of the present survey on an age group basis, with the break at nine years of age.

Table I presents the findings concerning hearing acuity in 100 allergic patients, 59 of whom were under nine years of age. In the total case load, 42 patients suffered some disturbance of hearing sensitivity. Of these, 33

were under nine years of age. Considered on a percentage basis, while 42 per cent of *all* patients showed a loss, in fact, 56 per cent of the patients *under nine years* had a loss, as compared with 22 per cent of those who were nine years old or older.

TABLE I
HEARING ACUITY OF 100 ALLERGIC PATIENTS - BY AGE

AGE GROUP	NORMAL	LOSS	% SHOWING LOSS
9 and over (41)	32	9	22%
under 9 yrs. (59)	26	33	56%
% distribution (100%)	(58%)	(42%)	

It had initially been determined to include in the study the first 100 allergic patients who were without infectious complications, who were old enough to give valid responses to standard pure-tone audiometry, and who would stay on until all diagnostic procedures and hearing tests had been completed. There was no screening according to the nature of the allergic syndrome. It therefore developed in the normal course of events, as illustrated in Table II, that although 82 patients had either perennial or seasonal allergic rhinitis included in the diagnosis, 18 patients lacked either of

TABLE II

A. HEARING LOSS RATE: BY DIAGNOSIS

DIAGNOSIS	NO. OF CASES	LOSS	% SHOWING LOSS
no allergic rhinitis	18	5	28%
includes all. rhinitis	82	37	45%

B. LOSS RATE IN 82 ALLERGIC RHINITIS PATIENTS - BY AGE

9 and over	35	6	17%
under 9 years	47	31	66%

these syndromes, presenting instead major symptoms of asthma, eczema, or urticaria either alone or in combinations. Nevertheless, five of these 18 showed a hearing disturbance. Recalling the 42 per cent of undifferentiated allergic patients with a hearing loss, we find a 45 per cent loss incidence among patients with allergic rhinitis and a 28 per cent loss incidence among patients lacking this diagnosis (Table II-A). Although the difference between these two groups is large, there is a higher incidence rate than one might expect amongst patients who have no allergic rhinitis. This finding calls for further investigation.

An evaluation of the 82 patients who had either seasonal or perennial allergic rhinitis revealed a finding of major significance (Table II-B). Of the 35 patients over nine years of age, six (17 per cent) showed disturbed acuity. But of the 47 who were less than nine years old, 31 (66 per cent) had hearing that was below normal (Table II-B).

TABLE III

ANALYSIS: 42 CASES OF HEARING IMPAIRMENT

TYPE OF LOSS	UNDER 9 YRS OLD		9 YRS AND OLDER		TOTALS	
	Number	%	Number	%	Number	%
Intermittent Loss	24	56%	5	12%	29	68%
Persistent Loss	9	23%	4	9%	13	32%
Totals	33	79%	9	21%	42	100%

Because series of tests had been performed on the same subjects, it was possible to compare findings not only from patient to patient, but within each patient's series, from test to test. The Wishik report, similarly based on a comparison of multiple tests, had stated: "Most of these children (who ever failed a hearing test) did not have continuous hearing loss . . . they failed . . . 49.3 per cent of the . . . tests they took . . . only 29 per cent of the (test) failing pupils . . . fell into the definition of continuous hearing defect." The present investigation has found that hearing loss was demonstrable in *all* tests in only 13 of the 42 patients showing a loss (Table III). Twenty-nine patients, or better than two-thirds of the loss cases, showed an intermittent loss of hearing which might or might not have been discovered on any single hearing test. Furthermore, the largest incidence of this intermittent type of hearing loss occurs in the age group that has least subjective ability to notice changes in personal fitness. As in the survey by Wishik, Kramm and Koch, approximately four-fifths of the cases of intermittent loss occur in children under nine years of age.

In other words, less than one-third of the patients suffering disturbances of hearing, those with persistent loss, would surely be found by usual hearing survey methods. Over two-thirds might go undiscovered. This is true because the usual procedure in school audiometric surveys is a single screening examination of all members of the test group, on a pass-fail basis. No further testing is done on those who rate "Pass." Individuals who fail the initial screening receive a detailed retest. Only those who fail both tests are referred for medical attention. If hearing acuity is normal on the second test, it is assumed that the screening test result was in error, or of merely transitory significance because of a "cold." Report forms upon which school systems base their understanding of pupil behavior routinely recognize only two possibilities: "Hearing Loss" and "No Hearing Loss." They reflect a continuing all-or-nothing attitude toward conflicting test results: "If a loss comes and goes, it does not exist." In view of the

quantity of testimony previously adduced here, these authors hold that any loss, reliably measured, which comes and goes most certainly must exist at the time it is noted, and not exist when it is not noted. If its existence conjoins the foreseeable, periodic exacerbations and remissions of a chronic disease, then the potential effects of its existence must be seriously considered.

For practical purposes, audiograms are interpreted in terms of their relation to the way in which a person is able to hear speech. Words are composed of sequences of sounds which, within a single word, differ widely from each other both in intensity and in range of vibratory frequency. A hearing disturbance rarely affects reception of all of these sounds equally. Some elements in a word may be heard perfectly, while the reception of others may be distorted or completely lacking. Similarly, within a phrase or a sentence, the accented syllables are those produced with relatively great sound energy. The "little" words which lace the sentence together meaningfully and those word endings which may indicate modifications of tense, number, or degree are usually produced with a minimum of intensity, and may not be heard at all when hearing acuity is diminished.

Up to this point, we have been discussing hearing disturbances and allergies, anatomy and the acoustic properties of speech. The time has come to talk about children. Learning is a child's total waking occupation and, although recognition and identification of his world will largely come to him through his eyes, understanding of it will for many years come to him only via his ears. An adult can "eavesdrop" visually—being able to read immediately makes available to him not only the accumulated recorded experience of mankind, but also the numberless trivial fragments of information which help him to maintain a functioning interactivity with the world around him. Until a child is skilled enough to use reading ability meaningfully, he depends totally upon spoken language for all information and communication. And before he can use spoken language, he must hear it. For an adult, whose vocabulary is well established and who has a normal reservoir of language experience, the partial, scattered, fluctuating obliterations of speech sounds which mark hearing disturbances, may be annoying, but they are seldom incapacitating. He is able to make up for them by an understanding of the context of the situation, and a memory of and familiarity with customary language usage. The young child has no such reservoir to draw upon. Daily, he is subject to a bombardment of new experiences and unfamiliar words. The degree of hearing loss which may be of little practical significance to an adult, can, therefore, become a substantial handicap to a child when it blocks the only channel through which so large an amount of learning must make its way.

In addition to this educational retardation, the quality of speech development and production may be affected. West[14] points out that "the effect of hard-of-hearing conditions upon speech depends, among other things, upon the age of the patient at the onset of the aural impairment."

In their study, "Effects of limited hearing on development of speech in children under three years of age," Huizing and Pollack[15] state: "The development of speech implies the learning by imitation of the basic phonemes and usually occurs between the ages of one and three. . . . Through constant visual and auditory stimulation, listening habits are established for all types of sound. These listening habits do not develop normally in children with limited hearing."

Reviewing data on 454 cases of speech retardation, in an attempt to establish etiology, Goodwin[16] found less than 5 per cent to have been caused by hearing loss, as determined by a single hearing evaluation. But he also lists 53 cases with a "functional" etiology and another 97 cases in which decision as to etiology had to be deferred. In fact, then, more than 33 per cent of these cases of speech retardation remained inexplicable in terms of mental retardation, brain damage, or demonstrated hearing loss. A similar situation maintains in every attempt to assess etiologic factors for the defective speech production of children. The word "functional" has gained some acceptance as a description of etiology. It is seldom recalled that in fact this term refers correctly only to the absence of structural defect, is a negative finding, and does not describe the cause of any phenomenon.

Let us consider the observations of West and Huizing, together with the present findings that 56 per cent of allergic patients under nine years of age suffer some impairment in hearing, and that two-thirds of these losses may escape detection. To these points, we add the findings of the Rapaport, Szanton and Appel investigation which established that 41 per cent of major allergic syndromes in a group of 5,152 individuals took onset before 4 years of age. To be considered also, is the fact that as the eustachian tubes develop, a chronic allergic illness which had caused vacuum or secretory otitis and hearing loss in the young child, may continue to exist in the older child with no attendant impairment of hearing. The continuing presence of poor speech patterns, learned and established in use at an age when listening habits were not developing normally, may remain as the only sign that "Kilroy was here." The authors believe that a substantial reduction could be achieved in the percentage of speech and language deviations now classified as "functional," through the use of medical investigation for the presence of allergic disease. Moreover, they recommend that school hearing tests be made and considered in a series, for every child who displays frequent irritations of the respiratory tract.

The Reading report,[1] which also investigated impact of hearing loss upon academic progress, shows that children "who ever had a hearing impairment during their school lives were twice as likely to repeat a grade as were other children." And "early in their school careers, the children who probably had had a hearing defect prior to admission to school were grossly retarded academically." It was found that "moderate unilateral impairment of hearing as well as severe or bilateral loss of hearing seemed

to constitute an educational handicap, especially during the early years of learning language, reading, and spelling, when missing parts of the sounds might almost completely prevent a child from grasping the meaning of what he hears."

For the pediatrician and for the allergist, these considerations must be related to the findings in this paper. A syndrome exists which will be termed allergic paracusis of childhood. It is most prevalent in the early years of life, affecting the hearing of 66 per cent of the children who present symptoms of allergic rhinitis and are under nine years of age. It is associated with vacuum otitis, is unaccompanied by pain, and is most frequently characterized by intermittency of hearing loss. Furthermore, even in those cases where loss is persistent, it is not static in degree, but manifests fluctuations in intensity, and variations in frequencies affected. Because of its variability and the youth of those in whom it most often occurs, its presence is rarely suspected, and behavioral disturbances attributable to it are frequently charged to "immaturity," "inattentiveness," "dullness," and "emotional insecurity." Recognition of allergic paracusis of childhood as a clinical entity will produce new answers to old questions in the fields of pediatrics, allergy, and otology, as well as in the associated disciplines of audiology, speech pathology and general education.

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314 Elizabeth Street

Historical Document
1920

A CASE OF HYPERSENSITIVENESS TO COW'S MILK

EDWARDS A. PARK, M.D.
Baltimore, Maryland

WHEN the substitution of a food containing cow's milk for a food not containing it is followed by vomiting and diarrhea, with perhaps other symptoms, it is easy to assume an idiosyncrasy which causes all food containing cow's milk, however intelligently administered, to act like a poison. In all probability, in a considerable number of the cases reported in the literature as examples of hypersensitiveness to cow's milk and a great proportion of those so regarded and treated in practice, the patients suffered merely from ordinary forms of indigestion. Hypersensitiveness to cow's milk has been made the subject of actual proof, like the hypersensitiveness to egg, to ragweed pollen, to pork, and to other substances through its transference to animals by injection with the patient's blood serum. Strong corroboratory evidence of its existence can be obtained if precipitins are found in the blood,† or by means of skin tests. Evidence of its existence, essentially the equivalent of proof, may be furnished by clinical data alone, namely, when the ingestion or introduction into the body of quantities of cow's milk altogether too minute to be attended by any consequences in any other condition is regularly followed by characteristic symptoms as in the case now to be described.

CASE REPORT

A.B.C., a boy, was born March 2, 1916, and is now three years of age.

Family History.—The aunt on the father's side believes that she has an idiosyncrasy to shellfish, inasmuch as she has twice developed severe urticaria a few hours after eating them. She has eaten shellfish on other occasions, however, without consequences. Both the paternal grandfather and great grandfather were subject all their lives to outbreaks of eczema of unexplained origin. With the exception of these facts the family history on the father's side has no possible bearing on the boy's illness. On the mother's side of the family among the great grandparents, grandparents, and an exceedingly large number of collaterals, no record of any illness which could be interpreted as hypersensitiviness to protein can be obtained. The parents of the patient are both well. Certainly neither has shown any form of protein hypersensitiveness so far as is known. The sister of the patient, 4½ years of age, has never been sick, except for an attack of otitis media, and certainly is not hypersensi-

Reprinted from *American Journal of Diseases of Children,* 19:46, 1920.

†The determination of precipitins to cow's milk in the blood of the patient is not sufficient alone to establish proof of a hypersensitiveness to cow's milk, because they have been found in the blood of marantic children who showed no evidence of hypersensitiveness to cow's milk.

tive to any of the ordinary foods. No member of the family on either parent's side, for four generations, including collaterals, has been subject to asthma or hay-fever.

The diet to which the mother had always been accustomed was not peculiar in any respect. She had never been in the habit of drinking milk, though she had taken it in tea and coffee, with cereal, and as an ingredient in her food. During her pregnancy she did not alter her usual diet, and during the few days which immediately succeeded the birth of the baby she took milk only in very moderate quantities.

Patient's History.—The birth of the baby was normal; the birth weight was 9¼ pounds. The labor lasted twelve hours and was not especially difficult. Physical examination shortly after birth revealed no abnormal condition. The baby was put to the breast on the second day, at six-hour intervals, and from the third day on was nursed at four-hour intervals. The flow of milk became established on the fourth day. The baby gained from the first at a normal rate. At the end of four months he weighed 17 pounds, and at the end of one year 23 pounds. Except for the illnesses about to be recorded he was never sick; he never vomited, never had loose stools, or showed any variation from the normal. In general his digestion seemed to be extraordinarily good. He had one or two normal stools a day with an almost perfect regularity.

First Two Attacks Following Ingestion of Cow's Milk.—April 13, 1916, when the baby was six weeks old, the 2 p.m. nursing was omitted and a bottle feeding, composed of 1 ounce of cow's milk, boiled for five minutes, 2 ounces of boiled water, and one-half a level teaspoonful of cane sugar was substituted. It cannot be found that the baby had ever received cow's milk previously.* Of this artificial feeding the baby refused all but 1 ounce, so that he swallowed altogether not more than 10 c.c. of cow's milk. Unfortunately, he was not carefully observed after the feeding had been given. It is known merely that he went to sleep, remained asleep for some time, and when roused by the nurse, vomited. He was excessively pale and "heavy." When offered the 6 p.m. nursing, he refused it and vomited again, and then once more fell into a heavy sleep. He took the 10 p.m. nursing, however. By the following morning he seemed much as usual.

Inasmuch as the attack of vomiting just mentioned had occurred without apparent cause, the possibility that the baby might be hypersensitive to cow's milk was considered. Accordingly, one month later (May 11, 1916) when the baby was 10 weeks old, a mixture of one teaspoonful of cow's milk, boiled for five minutes, and one teaspoonful of water was given with the special object of determining whether a quantity of cow's milk too small by any possibility to produce indigestion would cause a recurrence of the illness just described. The baby took only one teaspoonful of the mixture, and therefore swallowed only one-half teaspoonful of cow's milk. Immediately afterward he was put to the breast, which he took in a normal manner. Not very long after the nursing was finished the baby fell asleep. Occasionally he opened his eyes and several times he yawned. His face became flushed. At 5:55 p.m., four hours and fifty-five minutes after he had received the half teaspoonful of cow's milk, he vomited a small amount, and ten minutes later a large amount of bile-stained fluid. He had become exceedingly pale and seemed greatly prostrated. Shortly after the recurrence of the vomiting, he had two large loose stools containing mucus. Again he refused the 6 p.m. nursing, and slept heavily until 10 p.m., when he awoke and nursed in a normal manner. The following

*Although no record that the baby had received cow's milk at the maternity hospital where the mother was confined can be found, such a possibility cannot be excluded.

day he seemed to his mother to be pale and drowsy, but by the third day he was normal.

Skin Reaction to Milk.—Attempts at Demonstration of Hypersensitiveness to Cow's Milk by Skin Tests.—May 25, 1916, when the baby was 12 weeks old, an attempt to demonstrate local hypersensitiveness of the skin to cow's milk by means of scratch tests was made. A drop of a 1:10 dilution of cow's milk and one drop each of a 1:100 dilution of goat's milk and of distilled water, the two latter as control substances, were placed at well separated points on the leg and crossed linear scarifications of the skin were made through them by means of clean needles. Traumatic reactions followed immediately at all three points of injury, but a reaction in excess at the site of the scarification through the cow's milk did not develop. Although the cutaneous test with the cow's milk was negative, a delayed general reaction seemed to occur, for the baby fell into the drowsy state previously mentioned, and four hours after the test had been made, vomited and had two loose stools.**

At about this time a small quantity of goat's milk was fed to the child and produced no symptoms.

Intracutaneous Tests with Various Proteins with Resulting Attack.—May 28, 1916, the baby was taken to Johns Hopkins Hospital, and at 1 p.m. was given intracutaneous tests with a series of different protein substances (Table I) by Dr. K. D. Blackfan. Observations were made by Dr. Blackfan at five-minute intervals over a period of half an hour. An area of erythema and edema not exceeding 5 mm. in diameter appeared within the first five minutes at the sites of all the tests, but did not extend sufficiently around any one to make it possible to regard it as positive. At the end of the half hour's observation, at 1:30 p.m., the baby was taken home. During the drive home, the baby became much flushed and fell into a heavy sleep. At 3:30 p.m., three and one-half hours after the injections, he awoke, turned white, and vomited twice. He appeared to his mother to be very sick. At 4 p.m., when seen by a physician, he was pale, appeared greatly prostrated, and yawned repeatedly. The pulse was 150; respirations 48; rectal temperature 99.2 F. The respiratory murmur was normal. It was then observed that considerable induration, an area measuring roughly 1½ cm. in diameter, existed at the point of injection of the cow's milk, whereas none could be found at the points of injection of the other substances. Unfortunately, it is impossible to say at what time the local reaction at the point of injection of the cow's milk developed, because no observation was made between 2 p.m., the hour when the child left the hospital, and 4 p.m., when he was examined by a physician. The induration lasted a considerable time and was still present, though much diminished, the following morning. Following the

**In the well-known case of hypersensitiveness to buckwheat described by Smith a general reaction followed a local skin test. "The left arm was scarified in two places under strict antiseptic precautions. Without the patient's knowledge, an amount containing a grain of buckwheat was taken from a sterilized infusion of the cereal and rubbed into the upper scarification, while a mixture of sterile flour and water was applied to the lower one. The denuded areas were situated about three inches apart. . . . Within fifteen minutes after the vaccination the patient remarked, 'the buckwheat is beginning to work.' He complained of a 'tight feeling' in his chest, and of nausea in the 'pit of his stomach.' He began to cough at frequent intervals, and there was noted increase in the respiratory movements; asthmatic breath sounds; rapid pulse which soon became intermittent; suffusion of the conjunctivae; an erythema, more pronounced on the face, neck, forearms, hands, chest and back than on the buttocks, abdomen and lower extremities; intense pruritus; slight swelling of the features, hands and fingers; giddiness, restlessness and unsteadiness in the gait."

TABLE I. SHOWING RESULTS OF INTRACUTANEOUS TESTS WITH PROTEIN SUBSTANCES

	Period of Observation					
	5 Min.	10 Min.	15 Min.	20 Min.	25 Min.	30 Min.
Woman's milk undiluted†	No reaction‡	No reaction	No reaction	No reaction	No reaction	No reaction
Cow's milk 1:100 solution	No reaction	No reaction	No reaction	No reaction	No reaction	No reaction
Egg albumin 1:10 solution	No reaction	No reaction	No reaction	No reaction	No reaction	No reaction
Beef extract	No reaction	No reaction	No reaction	No reaction	No reaction	No reaction
Barley water	No reaction	No reaction	No reaction	No reaction	No reaction	No reaction
Horse serum 1:10 solution	No reaction	No reaction	No reaction	No reaction	No reaction	No reaction
Sterile water	No reaction	No reaction	No reaction	No reaction	No reaction	No reaction

†0.05 c.c. of each solution injected intracutaneously.

‡At the point of inoculation of each substance an area of erythma and edema not exceeding 5mm. in diameter appeared within the first five minutes but, as it did not increase, it was regarded as negative. No observation was made from 1:30 p.m., when Dr. Blackfan made his last observation, until 4 p.m. at the end of the acute attack, when child was seen by doctor. At this time a mass of induration measuring 2.5 cm. in diameter could be palpated about the point of injection of the cow's milk. It was still present the following morning.

attack the baby took the 6 p.m. and 10 p.m. feedings in a normal manner, but had two loose stools containing mucus.

Attack Following Feeding of Few Drops of Condensed Milk.—At 10 a.m., June 1, 1916, when the baby was 13 weeks old, he was given through a mistake, two to three drops of a solution of one part of condensed milk and twelve parts of water. Within half an hour after he had taken the condensed milk he became drowsy and slept for two hours and fifty minutes. The illness which followed may best be described in the words of the mother. "Waking he vomited violently yellowish green bile, no milk; turned very pale; began to take short panting breaths. His eyes rolled upward. His lips turned blue. He vomited again and lay exhausted. Turning again deathly white he vomited once more and panted for breath. He was too far gone to cry. His lips again turned blue. He vomited again and had a big green stool." The attack lasted forty-five minutes. The mother thought death was imminent. When the physician arrived, more than three-quarters of an hour after the commencement of the attack, the acute symptoms were virtually over. The child was exceedingly pale, and lying motionless on his back on a pillow, with head thrown back and eyes half open, and pupils lost to view beneath the upper lids, giving the impression of being extremely prostrated. The respirations were 46 to the minute but were not especially deep; the pulse was 150; rectal temperature 99.2 F. Examination of the heart, lungs and abdomen revealed no abnormal conditions; the breathing was not asthmatic; the reflexes were normal. Following these alarming symptoms the baby slept for one hour, but took and retained his 6 p.m. nursing. The following day he appeared to be well again except that he was pale and seemed tired.

In the latter part of August a goat was purchased, inasmuch as the supply of breast milk showed signs of failure, and September 30 the weaning from the breast to goat's milk was begun. The weaning, accomplished without difficulty or any event of importance, was complete November 2, when the baby was 8 months old.

Attack Resulting Probably from Ingestion of Bread Containing Cow's Milk.—On the morning of Oct. 31, 1916, when the mother lifted the baby out of the

crib, she found a large quanity of vomitus on the baby's pillow. Inasmuch as the baby had never vomited on a single occasion, except after the administration of cow's milk, as recorded above, it seemed not improbable that he might have received by accident cow's milk in his food of the previous evening. Although the greatest care was taken at the dairy farm at which the goat was kept, and at the baby's home where cow's milk was used for the other members of the family to prevent the entrance of cow's milk into his food, accidents of this nature could not be precluded absolutely. On telephoning to the dairy and on questioning the servants in regard to the preparation of the baby's food on the previous day, no evidence that the baby had received cow's milk could be found. A clue was finally supplied, however, by the cook, when she said that at 6 p.m. she had seen the baby eat a piece of baker's bread about as large "as the end of the thumb" given to him by his sister. On communicating with the bakery the information was obtained that milk had been used in the preparation of the bread. A week later the baby was given a piece of bread of a corresponding size made without milk, but manifested no symptoms.

Renewed Attempts at Demonstration of Hypersensitiveness of Cow's Milk.— Some time in the latter part of December (the exact date not recorded) another attempt to demonstrate hypersensitiveness to cow's milk by means of a skin test was made. The technic employed was this time that advised by Craig for the cutaneous test with tuberculin. A drop of cow's milk and of goat's milk were placed on the skin of the leg at the same distance from each other, and six or more punctures of the superficial portions of the skin made through them. The tests were started at 1:15 p.m. At 1:25 a.m. a wheal about 3 mm. in diameter had developed about each point of scarification surrounded by a faintly pink areola. The two test areas were observed for more than two hours, and though the inflammatory reaction around the test made through the cow's milk became slightly larger than that made through the goat's milk no well marked difference developed. Jan. 7, 1917, these tests with the cow's milk and goat's milk were repeated. Ten minutes after the tests had been made a tiny wheal surrounded by a faintly pink areola appeared about the scarification through the goat's milk, whereas an oval area of redness about 3 cm. long and 1.5 cm. wide, with considerable central induration, developed at the site of the test made through the cow's milk. Three-quarters of an hour after the tests had been made the red areola about the point of inoculation with the cow's milk had decreased slightly, but could be seen across the room, and could easily be palpated, whereas the reaction about the site of the goat's milk test remained essentially as before. No constitutional reaction of any sort was observed after these two cutaneous tests.

Desensitization to Cow's Milk.—Sept. 10, 1917, when the baby was 18 months of age, it was determined to make an attempt to desensitize him by the administration by mouth of minute quantities of cow's milk. Accordingly, at 8 a.m. with the morning feeding 0.001 c.c. of cow's milk was given. The baby showed no symptoms until the afternoon, when he became pale and appeared sick, lying down, refusing part of his food, and crying as if in pain. Becoming worse in the evening the temperature was taken and found to be 102 F. Examination revealed otitis media, fully explaining the baby's condition. Further attempts at desensitization were, therefore, deferred. The baby recovered from the otitis media in about two weeks, but remained pale, and appeared to lack his former vigor for several weeks afterward.

Nov. 4, 1917, the attempts at desensitization were renewed. The baby was now 20 months of age. He had begun to stand at the age of 12 months, and to crawl vigorously at 15 months, but had not walked alone until 18 months. As soon as

he was able to crawl from one part of the house to another, and particularly after he had learned to walk, it had become increasingly difficult to safeguard him against the ingestion of food containing cow's milk. On a number of occasions he had succeeded in obtaining crumbs of baker's bread and more than once bits of buttered toast which had fallen on the dining room floor or had been given to him by his sister, who seemed bent on bringing about his discomfiture whenever possible. In spite of the fact that the particles of food which he succeeded in eating often must have contained traces of cow's milk he had not once become sick. It seemed probable, therefore, that he had partially at least desensitized himself, or had begun to outgrow his hypersensitiveness. Accordingly, it was determined to administer one drop of undiluted cow's milk as an initial dose. Nov. 4, 1917, this was done; at 8:40 a.m. one drop of cow's milk was given followed immediately by breakfast. After the ingestion of the one drop of cow's milk no effect was noted. There was no drowsiness or vomiting and the pulse remained unaltered. November 5, two drops were given at 8:20 a.m. with the breakfast without the production of any change in the baby's condition. On November 6, at 8:20 a.m., four drops were administered with the breakfast. At 9:30 a.m., the baby, who had been playing about the dining room table, suddenly stopped, turned pale, and lay down on the floor on his side with his head on the rug, which he had never done previously. He was immediately taken up and put to bed, where he slept for some time. He did not vomit. The rectal temperature was 99.2 F. November 7 he was given five drops of cow's milk at 8 a.m. At 9:15 a.m. he again became pale, stopped his play, and lay down on the dining room floor. He was again placed in his crib, but at the end of an hour seemed to have recovered entirely. His temperature remained normal and no vomiting occurred. November 8 he was given ten drops of cow's milk with his breakfast at 8:15 a.m. At 9:15 a.m. it was noticed that he had turned pale, and at 9:30 a.m. he went to sleep for half an hour. Ordinarily he never became sleepy at this time. November 9 he was given fifteen drops with his breakfast at 8:15 a.m. At 9:15 a.m. he appeared paler than previously, but did not become drowsy. November 10 he was given thirty drops at 8 a.m., and November 11, sixty drops, but showed no symptoms. November 12 he received 7.5 c.c. of cow's milk at 8:15 a.m. At 9:50 a.m. he appeared pale, went to his nurse, lay on her lap for ten minutes very quietly, then climbed down again and began to play in a normal manner. November 13 he received 10 c.c. without the production of any symptoms. From November 13 on, he showed no symptoms after the ingestion of quantities of cow's milk, which were steadily increased first by 1 c.c. daily (November 16 he received 14 c.c.), then by 2 c.c. (November 17 he received 16 c.c.), and finally by the addition of 3 c.c. (December 1 he received 60 c.c.). December 2 he was given a cup of cow's milk instead of goat's milk, and by December 10 he took one-half liter, the goat's milk being omitted altogether.

Present Condition.—Now, at three years of age, the child is perfectly well. He drinks regularly a pint of cow's milk daily. He does not dislike his milk, but does not care for it especially, always drinking water in preference to it, and regularly leaving it until the last. He has had another attack of otitis media, and a few days ago on coming from Florida to his home in Baltimore he broke out with an eczematous eruption which could not be explained. He has had no recurrence of symptoms such as have been described. It is certain that the child is not affected by egg.

COMMENTS

Perhaps the most unusual feature of the case was the delay in the development of the anaphylactic response, which in the early period did

TABLE II. IMPORTANT DATA IN REGARD TO REACTIONS OF PATIENT TO COW'S MILK

Date	Age	Quantity of Milk	Mode of Administration	Interval Between Entrance of Milk Into Body and Full Development of Symptoms	Symptoms
4/13/16	6 wks.	⅛ oz.	Mouth	3½ to 4 hrs.	Pallor, drowsiness, vomiting
5/11/16	10 wks.	½ teaspoonful	Mouth	4 hrs. 55 min.	Drowsiness, flushed face, yawning, vomiting, prostration, diarrhea
5/25/16	12 wks.	One drop of a 1:100 solution	Skin (scarification)	4 hrs.	Drowsiness, vomiting, diarrhea
5/28/16	12½ wks.	0.01 c.c.	Skin (intradermal injec.)	3½ hrs.	Local induration of skin at site of test; drowsiness, flushing of face, later pallor, vomiting, yawning, prostration, diarrhea
6/1/16	13 wks.	2 to 3 drops sweetened condensed milk	Mouth	2 hrs. 50 min.	Drowsiness, repeated vomiting, pallor, dyspnea, cyanosis of lips, great prostration, diarrhea
11/6/17	20 mos.	4 drops	Mouth	1 hr. 10 min.	Pallor, drowsiness, faintness, no vomiting
11/7/17	20 mos.	5 drops	Mouth	1 hr. 15 min.	Pallor, drowsines, faintness, no vomiting
11/12/17	20 mos.	7.5 c.c.	Mouth	1 hr. 35 min.	Pallor, drowsiness, faintness

not reach its climax (as indicated by the act of vomiting) for from three to more than four and one-half hours after the ingestion of the cow's milk, and not for three and one-half hours after its introduction under the skin. It does not seem probable that the delay was caused by slow passage through the gastrointestinal tract or slow absorption, because the same delay occurred after the injection of the milk into the skin. The data at hand are too limited, however, to permit speculation.

Another interesting feature of the case is that the sensitiveness, though apparently exceedingly marked in the earlier months of life, exhibited a tendency to disappear spontaneously rather early. As already pointed out, however, the child may have succeeded in desensitizing himself to a certain extent when he became old enough to crawl about and find crumbs of food sometimes undoubtedly containing traces of cow's milk. The interval between the time of ingestion of the milk and the full development of the symptoms also seemed to diminish as the child became older (Table 2). When desensitization was begun at the age of 20 months, it will be remembered, the symptoms appeared within an hour and one quarter if at all. It was impossible to determine exactly at what moment the reaction began, and, therefore, the true incubation interval could not be measured. As has happened in the experience of others, the cutaneous tests failed to give clear indication of the actual condition. The single intradermal test did, however, give an unequivocal reaction which was late in develop-

ment like the symptoms. It indicated that the subcutaneous tissues or blood possessed the capacity to react in the presence of a sufficient concentration of antigen. Only in one of the attacks were symptoms present which indicated that the reaction had extended beyond the gastro-intestinal tract and involved other parts of the body, namely, the attack of June 1 which followed the ingestion of three drops of condensed milk. On that occasion, it will be recalled, severe respiratory symptoms were present. On all other occasions the clinical manifestations were limited to drowsiness, flushing of the face, yawning, later pallor, vomiting, prostration, anorexia and diarrhea. Though the reaction may have been systemic, there never was any clinical indication that such must be the case, with the exception, perhaps, of the attack of June 1 to which reference has just been made.

There was never any depression of the temperature. Moreover, the child, so far as is known, never passed into an anti-anaphylactic state. The reaction of May 11 did not prevent the reaction of May 25 from taking place, and the severe reaction of May 28 did not prevent the still more severe reaction of June 1 from occurring. It seems necessary to assume either that the provocative dose of cow's milk was insufficient to produce a systematic reaction of sufficient magnitude to confer temporary immunity, or else that the reaction was essentially a local one, limited to the gastro-intestinal tract. Again, however, speculation is not justified.

The existence of hypersensitiveness to cow's milk in an infant of six weeks who had never been known to receive cow's milk previously makes it necessary to regard the condition as prenatal in origin. The possibility that the hypersensitiveness was derived passively from the mother is excluded, if for no other reason, by its duration. In the absence of evidence that the peculiarity was acquired it must be regarded as having been inherent in the germ plasm.

ACKNOWLEDGMENT

The writer wishes to express his thanks to Professor Howland and to Dr. K. D. Blackfan and Dr. G. Powers for their advice and assistance.

EDITOR'S NOTE: Due to the limitation of space, some of the original references have been omitted.

THE STUDY OF TRUTH

For myself I found I was fitted for nothing so well as for the study of Truth; as having a mind nimble and versatile enough to catch the resemblance of things (which is the chief point), and at the same time steady enough to fix and distinguish their subtler differences: as being gifted by nature with desire to seek, patience to doubt, fondness to meditate, slowness to assert, readiness to reconsider, carefulness to dispose and set in order: and as being a man that neither affects what is new nor admires what is old, and that hates every kind of imposture.—FRANCIS BACON 1561-1626, *Essays or Counsels, Civil and Moral.* London: Simpkin Marshall, 1918.

Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

THE UNDERPRIVILEGED CHILD

Where Are We in Pediatric Allergy?

Within recent years, it has become evident that the incidence of allergy in childhood is larger than has been suspected. Several recent surveys indicate that as many as one out of every five children up to the age of fifteen has, at one time or another, shown some manifestation of major allergic illness. If the so-called minor conditions were included, the number of known allergic children would perhaps be as high as 50 per cent.

These are underprivileged children—children who are being denied a proper opportunity to grow and develop. Many miss a good part of their education either through absenteeism, poor physical condition, or because of hearing loss and associated learning difficulties; many are unable to participate in group activities or sports, or else they learn to fear any endeavor that involves physical effort; many become afraid to venture into any new situation where the risk of discovering new trauma awaits them.

Allergy is the major chronic illness of childhood. One survey of more than 6,000 children completed last year (and reported in *The Pennsylvania Medical Journal* of May, 1961) showed a 23.7 per cent incidence of major allergic disease in children below the age of fifteen. Of these allergic children, less than half had received treatment of any sort. Whether or not much of this treatment was adequate can be judged from some of the medications prescribed: aspirin, tranquilizers, sedatives, antihistaminic agents, et cetera.

The reasons for this unfortunate situation are complex; the unhappy result is the underprivileged allergic child. We know that education in allergy is inadequate at all stages of medical training—school, internship, and residency—as well as in direct teaching of the lay public. Only 40 per cent of the medical schools in this country provide what they consider adequate training in allergy. We know that allergy is still sometimes extremely difficult to diagnose or treat. We know that until recently our tools were relatively crude, our knowledge relatively limited. Nevertheless, much progress has been made, much knowledge and skill gained. The problem of allergy is, slowly but surely, being solved.

Interest in allergy among young physicians is high. This has been reflected by my own experience at a large municipal hospital center, where members of the house staff are assigned to my pediatric allergy clinic for

periods of four to eight weeks. For some, with a background of nothing more than a one-hour lecture, it represents the first actual exposure to the practical problems of allergic illness. Others may have had several hours of lectures, but none has had the opportunity to do an evaluation of an allergic patient, none has had practical experience with skin testing, none would be able to develop a program of hyposensitization on the basis of test results, or to treat an allergic patient over an extended period of time. Given the opportunity to learn, many of these young physicians express a surprising interest and eagerness.

There is also an active interest in allergy among older physicians. This has been demonstrated at several recent seminars in which I have participated, where attendance and interest on the part of non-allergists have been consistently high. Most of these physicians are well aware of the size of the allergic problem in their own practices, but many frankly don't know how to handle it beyond providing symptomatic medications. There is a basic lack of orientation in allergy, an unawareness of the chronic nature of allergic illness, a general ignorance of the obstacles that may be encountered, and a failure to understand the need for long-term, total treatment, sometimes including psychiatric measures. In short, there is an obvious and surprisingly wide gap between interest in allergy, on the one hand, and practical knowledge of how to deal with it, on the other.

The biggest loser in this unfortunate situation is the underprivileged child —that is, the child with untreated or inadequately treated allergy. His schooling suffers, his family suffers, his physical development suffers, and sometimes his mental health suffers. Often, life in the home of the allergic child deteriorates into little more than a background for the constant struggle, emotional as well as financial, against chronic, undiagnosed illness. Complex problems deserve simple solutions. The answer to the problem of the allergic child is not simple, nor is it entirely clear that either the medical profession or the public at large is now ready to come to grips with that problem. As physicians, however, and as allergists, it is upon us that the burden for action falls.

Hopefully, more medical schools will find it feasible to increase the time available for their students to participate actively in a more practical and more extensive demonstration of the nature and treatment of allergic illness.

Hopefully, public health and information agencies will find the means to further inform the people of the treatment available to the allergic patient, and the particular value of treating allergy when it first appears in children.

Perhaps an important part of the solution is that we all need to display a little missionary zeal. Allergy in childhood can be treated successfully. Let's give the underprivileged kid a break.

HGR

Progress in Allergy

MICROBIAL ALLERGY

A Critical Review—1950-1960

HERMANN BLATT, M.D., F.A.C.A.
Cincinnati, Ohio

(Section I, Continued from September Number)

NATURE OF THE IMMUNOLOGIC INADEQUACY OF NEO-NATAL RABBITS

Dixon and Weigle[68] undertook experiments to find out whether the lymphoid cells of the neo-natal rabbit would be capable of forming antibody if they were removed from the neo-natal environment. They exposed splenic cells from neo-natal rabbits to antigen *in vitro* and then transferred them to either adult x-radiated or intact neo-natal rabbits. They found that neo-natal cells were capable of producing considerable amounts of antibody in the adult recipients, but not in the neo-natal recipients. For comparison, they also transferred adult sensitized lymphoid cells to neo-natal and x-rayed adult recipients. In agreement with their earlier findings, they observed far better responses in the adult recipients than in neo-natals. After transference to x-rayed adult recipients, both *in vitro* sensitized neo-natal lymphoid cells and *in vivo* sensitized adult lymphoid cells made much more antibody than after transference to neo-natal recipients. The reason for such a poor response by sensitized cells transferred to neo-natal recipients under the experimental conditions employed by these investigators is not yet clear. Nevertheless, Dixon and Weigle point out that neither neo-natal cells sensitized *in vitro*, nor adult cells sensitized *in vitro* form antibody well after transfer to neo-natal recipients. This fact might be due to difficulties in the neo-natal recipient, and not in the transferred cells, or the method of immunization. Moreover, investigators have previously suggested that the neo-natal recipient may reject the transfer cells before they can make an immune response.

"The relatively poor formation of antibody by specifically sensitized cells transferred to neo-natal rabbits under the experimental conditions employed here, might seem to contradict several experiments demonstrating antibody formation by adult lymphoid cells in the neo-natal recipient."

RELATIONSHIP OF SPECIFIC BACTERIAL COMPONENTS TO THE ALLERGIC RESPONSE

The importance of separating the various chemical components of bacteria and studying each of these substances in its relationship to sensitization cannot be overemphasized. A better knowledge of such a relationship is necessary not only if we are to obtain superior antigens for desensitization, but also if we are to obtain better therapeutic results. Thus, it is our hope that more and more interest in this field of research can be stimulated.

Probably the organism most commonly studied is the tubercle bacillus. As early as 1923, Zinsser[69] made immunologic studies with purified tubercle polysaccharides, and more recently, Iland and Peacock[70] have carried out extensive studies concerning the serology of the tubercle polysaccharides. These authors concluded that, with our present state of knowledge, all the tubercle polysaccharides seem to have the same single hapten, and that "antibodies reacting with this hapten are rarely found in the sera of tuberculous humans, although they can easily be produced by injecting experimental animals with dead bacilli."

Dworetzky, Baldwin, and Smart[71] have continued to study the biologic effects of various material derived from staphylococcus. They demonstrated that extracts of *Staphylococcus aureus*, washed free of culture filtrate, produced markedly different results upon the isolated ileum of guinea pigs, as well as of intact guinea pigs and rabbits, than those of bacteria-free staphylococcic filtrate. Culture filtrate was shown to have lethal, hemolytic and dermonecrotoxic properties, not found in bacterial extract, for intact rabbits and guinea pigs. Both bacterial extract and culture filtrates were found to have toxic effects upon isolated ileum, but with a noticeable difference. First of all, the bacterial extract produced a typical anaphylactoid reaction, while the culture filtrate produced an irreversible contraction. Moreover, while the toxic effect of bacterial extract was heat stable, the effect of the culture filtrate was heat labile. As a result, studies with culture filtrate alone may overlook important toxic and allergenic factors within the cellular structure of these bacteria. These authors have now demonstrated a heat-stable factor in human, horse, rabbit, bovine, and guinea pig serum, which protects the isolated guinea pig ileum against the anaphylactoid effect of this fraction from *Staphylococcus aureus* organisms. Among the serums studied, it failed to protect only in the case of rat serum. Occurring within the gamma globulin fraction, this protective effect seems to be specific. Since gamma globulin protects the ileum against the anaphylactoid effect of the nucleoprotein and allows anaphylaxis to occur, it may make it possible, in the opinion of these investigators, to demonstrate anaphylaxis in guinea pigs that were rendered sensitive to this primarily toxic fraction.

Using the agar precipitin method, Beiser, Dworetzky, Smart and Baldwin[72] showed that human sera contained antibodies directed against both culture filtrates and bacterial extracts of Staphylococci, although most of the antibodies were directed against culture filtrates. All of the *Staphylococcus aureus* strains produced antigens which reacted with human gamma globulin, while only two out of nine *Staphylococcus albus* strains produced antigens reacting with human gamma globulin. This suggested a relationship between the pathogenicity of a strain of staphylococcus and its ability to stimulate antibody production.

In the same study of these authors, demonstrations showing anaphylaxis were also carried out. Anaphylaxis to a primarily toxic nucleoprotein fraction derived from washed ground hemolytic *Staphylococcus aureus* (F-10) organisms was demonstrated in the isolated segment of guinea pig ileum. The ileum segment was challenged with nucleoprotein fraction in the presence of pooled human gamma globulin. Anaphylaxis was also demonstrated with a similarly obtained nontoxic protein fraction from a strain (F-7) of *Staphylococcus albus*. These two demonstrations showed that the nucleoprotein fraction from the *albus* strain was more allergenic than that from the *aureus* strain. Furthermore, segments of ileum from guinea pigs sensitized to either fraction reacted anaphylactically to each other. Cross anaphylaxis and desensitization to the heterologous fraction resulted in complete or partial desensitization to the homologous fraction. These fractions, therefore, although derived from dissimilar strains of staphylococcus, seem to be immunologically closely related.

The relationship of polysaccharides to hypersensitivity, as it concerns those from animal parasites, has recently been reviewed by José Oliver Gonzáles.[73] This review presents evidence indicating that polysaccharides may be associated with hypersensitivity, as well as harmful to the host. While these investigations are, as yet, very meager, the findings thus far reported show clearly that further research in this field may reveal im-

portant data bearing on the role of polysaccharides in the production of allergy. Various problems are involved, but one of the most important is whether these polysaccharides are actually species-specific or whether they represent a common antigen.

The study of C. A. Stetson, Jr.[74] on the cutaneous, ophthalmic, and systemic reactions of normal rabbits to Gram-negative bacterial endotoxin presented evidence of the similarities of these reactions to the classic response of bacterial hypersensitivity. It has also been shown that the Shwartzman phenomena can be reproduced with tuberculin in BCG-vaccinated animals, as well as with suspension of heat-killed extracts of group A streptococci, in rabbits sensitized to these bacteria. It is Stetson's belief that these findings imply that the biologic activities of endotoxins may be based on the existence in normal animals of the delayed type of hypersensitivity.

During the past few years, Swineford[75] has been reporting his observations on various aspects of desensitization with bacterial haptens. Recently, he studied the problem of local desensitization and resensitization. His conclusion was that antisera confirms the presence of multiple passive sensitization to guinea pigs, so that they will react to and be desensitized specifically by aerosols or intra-abdominal injections of each hapten, one at a time. And although anaphylaxis followed intravenous injections of the serum, he was unable to elicit reverse passive anaphylactic reactions to nebulized antiserum. Swineford also found that locally desensitized bronchi could usually be resensitized by repeating the intra-abdominal dose of sensitizing antiserum, but for subsequent resensitization larger amounts of intra-abdominal antiserum were required. Some, but not all, animals sensitized passively with large amounts of antisera became spontaneously resensitized locally in two to seven days, after having been effectively desensitized locally.

MECHANISM OF ACTION OF THE TOXIC BACTERIAL ANTIGEN

According to Braude,[76] the clinical disturbances induced by Gram-negative bacteria take two forms, irrespective of species: (1) The overwhelming effects of a chief infection. This is characterized by fever, shock, diarrhea, muscular pains, leukocytosis, and they are found in patients with fulminating meningococcemia, coliform septicemia, severe dysentery, peritonitis, and transfusion reactions from contaminated blood. (2) Mild but persistent manifestations of such chronic infections as typhoid fever, brucellosis, pyelonephritis, and tularemia. Many of these disturbances can be reproduced by injecting washed dead bacteria. This has been attributed to a toxic agent within a bacterial cell and designated endotoxin. The toxic agent is a lipopolysaccharide and can be separated from the bacterial cell of Gram-negative bacteria. It is absent in Gram-positive bacteria. Although extensive studies have been carried out in the last few years as to the toxic activity of Gram-negative bacteria, mostly only crude preparations were used. When purified lipopolysaccharides were used, clinical effects were reproduced as seen in infections due to the bacteria from which they were isolated. Since these lipopolysaccharides are specific antigens, Braude decided to determine whether any or all of their physiologic effects result from immunologic reaction *in vivo*. He recently reported his five years of investigations. He prepared a well standardized purified toxin from *Escherichia coli*. This was grown on a basal synthetic medium and therefore permitted extraction of the purified lipopolysaccharide free of the impurities generally found in more complex media and in agar. He also developed a technique for preparing radioactive endotoxin by labeling with

radiochromium. Experiments were conducted, correlating the physiologic effects with the tissue localization of endotoxin in susceptible and immunized or tolerant animals. It was found that following intravenous injections of lethal doses, latent endotoxin was present in the plasma but not in the erythrocytes and then rapidly passed mainly to the buffy coat and to the liver. Brain or vasomotor centers were not stimulated directly by the endotoxin. Apparently, these centers are stimulated by an intermediate mechanism which the action of endotoxin sets off. Resistance to lethal doses of toxin generally depended on rapid plasma clearance and heavy hepatic localization of endotoxin.

Studies were made of certain specific actions of endotoxin, especially those on the reticuloendothelial system, on the circulating leukocytes, and on the heat regulatory apparatus. Studies were carried out to clarify the nature of acquired resistance to endotoxin. This was done by examining the metabolism of endotoxin in the tissues of immunized animals and by observing the role of tolerance in recovery from experimental infections.

Braude found that large doses of endotoxin produced two types of injury to the reticuloendothelial system, an immediate injury after injection of massive doses, and a delayed injury from large sub-lethal doses which become apparent only when the dose is repeated in twenty-four hours. Evidently the endotoxin produced a leukophoresis by localizing in the buffy coat and driving cells out of the circulation. This seemed to result in the stimulation of the neutrophilic reserves after only one exposure to endotoxin, so that circulating leukocytes were replenished thereafter about four times faster than normal. During the production of tolerance, the repeated injection of endotoxin led to an increasingly rapid respiration of neutrophils from the marrow to the circulation. The febrile response to endotoxin was also studied. Since fever in humans is never sustained without neurologic injury, despite the steady stimulus of specific infection, Braude postulated that the heat centers become non-responsive following a spike of fever. He supported this concept by showing that rabbits become refractory to the febrile effects of endotoxin for twenty-four hours after a single injection of endotoxin. This refractory state could be divided into two parts: (1) an early absolute refractive period during which no fever could be produced irrespective of the size of the second dose of endotoxin; (2) a relative refractory period which appeared after the initial febrile paroxysm had subsided. During this period, the attenuated response could be overcome only by giving a dose of endotoxin several times larger than the original one.

In humans, it seems that endogenous neutrophilic pyrogen is necessary for febrile reaction. This was discovered by intravenous injection of typhoid vaccine in normal persons and those with myelogenous and lymphatic leukemia. Patients with lymphatic leukemia usually failed to develop fever even after receiving 50 million dead typhoid-paratyphoid bacilli.

Tolerance results from repeated injections of small doses of endotoxin and is manifested by lessened susceptibility to the febrile leukopenic and lethal effects of endotoxin. Tolerance it was felt was merely a perpetuation of the refractory state which exists up to twenty-four hours after a single injection of endotoxin. It evidently was independent of the clearance rate of radioactive pyrogen from the blood. Tolerance to the lethal effect was dependent on the increased ability of the hepatic reticuloendothelial system to remove massive doses from the blood. Tolerance to the neutropenic effect was dependent on the accelerated rate of replenishment of neutrophils from the marrow. These studies gave some insight into the mechanisms involved in the various physiologic changes caused by endotoxin. Braude used a differ-

ent approach for examining the nature of the exact stimulus responsible for such changes. He conducted a series of experiments with the lipopolysaccharide endotoxin of *E. coli* to determine whether or not any of the reactions to endotoxin might be on the basis of reaction between antigen and antibody *in vivo*. These experiments were performed in normal persons and animals and compared with the results obtained in infected persons with *E. coli*. Intradermal reactions were studied by injecting 0.1 mg of *E. coli* lipopolysaccharide. This dosage was selected because it approximated the amount of purified protein derivative (PPD) generally used in tuberculin testing, and therefore permitted a comparison of reactivity to the two antigens under conditions of similar dosage. One hundred and one adults were tested; all gave dermal reactions, sometimes with lymphangitis, fever and arthralgia. The reaction was characterized by erythema and painful edema following two hours after the injection and reaching a maximum in twelve hours, and completely subsiding within forty-eight hours. In this group of patients were not only those infected by *E. coli* but some had immunologic disorders, such as sarcoidosis. One child had agammaglobulinemia; this child sustained high fever and had a marked systemic reaction. Most children gave milder reactions than adults. No precipitating neutralizing or complement-fixing antibodies were demonstrated for the *E. coli* lipopolysaccharide in normal human sera, or in those with *E. coli* infections. The antigen, however, gave strong complement-fixation and definite precipitation in the sera of immunized rabbits and rats. Different strains of *E. coli* endotoxin had been used, and they produced antibodies for heterologous endotoxin in the subjects studied, and therefore it is not likely that the negative serologic test in humans could be explained by antigenic differences among the infecting strains of *E. coli*. In view of this, Braude infected rats with *E. coli* by establishing pyelonephritis, and examined them for antibody to the lipopolysaccharide extracted from the infecting strain. The pyelonephritis was induced by intracardiac inoculation of bacteria and followed immediately by bilateral renal massage through the intact abdominal wall. Upon recovery from infection, all rats were free of circulating antibody. Skin tests were not performed on rats with *E. coli* pyelonephritis; however, specific immunologic tissue reaction to endotoxin was demonstrated. Since in man and animals, the tissue-hypersensitivity to endotoxin occurs without demonstrable circulating antibody, Braude believes that this hypersensitivity is analogous to that of tuberculin. The results of his experiments indicate that the effects of *E. coli* endotoxin are the result of a specific immunologic reactivity which all children acquire very soon after birth, and that it is like tuberculin sensitivity with respect to growth and microscopic appearance of skin reactions, passive transfer through leukocytes, and absence of detecting circulating antibodies by ordinary tests; but unlike tuberculin sensitivity it is not associated with resistance to infection. Braude concludes, "It is unlikely, however, that the lipopolysaccharides are devoid of primary toxicity. Instead, it would appear from the studies of Abernathy that endotoxin, like certain exotoxin, can elicit reactions in patients through both toxic and immune mechanisms."

EXPERIMENTAL STREPTOCOCCAL INFECTION IN THE RHESUS MONKEY

Vanace[77] presented a preliminary report on his observations in attempting to produce in the Rhesus monkey (*Macaca mulatto*), the pathologic counterpart of rheumatic fever by means of one pharyngeal injection with Group A beta hemolytic streptococci. He first did a pilot study of the normal

spectrum of streptococcal antibody titers and cardiac histopathologic alterations occurring in a control group of thirty-six Rhesus monkeys.

Serum levels of three streptococcal antibodies in this control group showed that this species of animal was susceptible to infections with the streptococcus. Myocardial lesions developed in 50 per cent of this control group. They did not resemble Aschoff's bodies.

Ten normal Rhesus monkeys were used for the experiment. During a control period of observation, normal values for a number of acute phase reactants were determined. Five animals were inoculated with type 15 streptococci, and five with type 12. At regular intervals, a number of laboratory tests for evidence of infection and cardiac tissue damage were carried out. At specified intervals, an animal was sacrificed and sections of the heart were examined with various special stains for evidence of tissue alterations.

One monkey sustained an active, and six monkeys a sub-clinical, infection. Seven monkeys demonstrated at least a two-tube dilution rise over control levels of one or more antistreptococcal titers. The antibody response to streptococcal infection as regards time sequence, beginning rise, maximal level, and duration of response, was similar to that of man. An animal that was not sacrificed developed a pharyngeal carrier of the injected streptococcus of eight months' duration. The cardiac tissue studies showed no quantitative or qualitative differences from the control normal monkeys. Neither were Aschoff's bodies produced.

TUBERCULIN ALLERGY

Tuberculin Reaction. The tuberculin test still remains, as Stein and Hetherington describe it, "the cornerstone in the control of tuberculosis." In this year's *Journal of the American Medical Association*[78] they published their fifteen years' experience with the tuberculin test, having tested 22,014 patients. Since the standard two-dose test proved highly satisfactory, they advise that it should not be modified in clinics serving areas where tuberculosis continues to be a major health problem. Perhaps the survey of Stein and Hetherington will make some clinicians more conscious of the practical value of the tuberculin test, since too many still have the erroneous idea that the test in adults has no value whatsoever.

At the Children's Hospital in Fuerzerradvany in Hungary, Rusti[79] has for some time been studying (1) whether tuberculin-positive sick children react differently to subcutaneous doses of tuberculin than do tuberculin-positive children who are not clinically ill; (2) whether the tuberculin intolerance or the threshold of the tuberculin stimulus changes as a result of treatment, or if there is a change in the phase (Phasenwechsel) between sensitization or desensitization; (3) whether x-ray of clinical changes takes place during treatment; (4) if there is a difference when tuberculostatic drugs are administered. Rusti found that in tuberculous individuals, tuberculin allergy can be changed artificially, as sensitization can be altered to desensitization by carefully prescribed subcutaneous tuberculin injections. "This altered condition, i.e., the enhanced tuberculin resistance, is therapeutically of the greatest importance, and seems to be due to the presence of an anti-allergic antibody." If tuberculin treatment is discontinued, the "enhanced resistance" lasts only a short time, although it may again be produced by repeating the treatment. The existence of a hypothetic anti-allergic antibody receives further support by passive transfer and "allergometric investigations" in man. When high tuberculin resistance is achieved

by artificial desensitization, the organisms react at the site of the tuberculin injection by forming real granulation tissue, that is, an abacillary tubercle.

Edwards and co-workers[80] skin-tested more than 3,200 students in Mongomery County, Maryland, during the spring term of 1957, with tuberculin and histoplasmin. The intradermal skin tests were given by injections of a 5 TU dose of standardized tuberculin and a 1:100 dilution of histoplasmin H-42. The reactions were read at forty-eight and seventy-two-hour intervals by measuring the transverse diameter of induration, while the photofluorograms of the chest were read without knowledge of the skin test results. It was found that tuberculin sensitivity was very low among white students throughout the county, with only 3 per cent having reactions indicative of a tuberculous infection. Histoplasmin sensitivity was much more prevalent than tuberculin sensitivity, and there were striking differences in sections of the county no more than 20 miles apart. Such differences ranged from about 14 per cent in the suburban schools in the Southeast to more than 60 per cent in the rural Northwest. Pulmonary calcifications were most frequently associated with sensitivity to histoplasmin, and sometimes with sensitivity to histoplasmin and tuberculin. In no instance was there sensitivity only to tuberculin.

In 1956 Palmer[81] made a survey of 120,000 young adults and found positive tuberculin reactions to be less than 10 per cent over most of the country. He points out that new tests are necessary to distinguish specific from nonspecific reactions, and although I will agee with him here, this is no justification for the fact that tuberculin tests have been in disrepute for the past several years. The test remains a valuable means of identifying infected individuals, as Palmer recognizes.

Indeed, Furcolow[82] recommends more extensive use of the tuberculin test, and where indicated, skin tests for histoplasmin, blastomycin and coccidiodin. Cowan reported a new one-test dose material for determining the tuberculin reaction which is a dilution of Old Tuberculin 0.1 cc. This is equivalent not only to 0.000005 cc of the U.S. Reference O.T. but also to 0.0001 mg PPD-S or five tuberculin units of PPD-S. This dose elicits reactions in most individuals having active tuberculosis, and is suitable for separating infected from uninfected children and adults. The intradermal injection of this material produces reactions in those harboring tubercle bacilli without any appreciable number of false positives. The reliability of the test thus makes it possible to screen out those individuals who are actual or potential victims of tuberculosis.

Since 1952, Tsow Pag-Chu and Li Chiu-Kao[83] have been using killed BCG vaccine as tuberculin testing material instead of Old Tuberculin. Performing over 10,000 tests, they found that the BCG material was more sensitive and gave less severe reactions. BCG vaccine 50 mg per ml, which could be kept indefinitely, was placed in a water bath at 60° C for one hour. On testing, one drop of the killed vaccine was put on the skin previously cleaned with alcohol. On the third to sixth day, a large sewing needle was pressed firmly over this spot. An area of induration of 1 mm or more was considered positive. Among the children who had been previously vaccinated with BCG, 16.9 per cent gave positive Mantoux tests and 31.8 per cent showed positive reactions with killed BCG vaccine. Three hundred sixty-five postvaccinated children (sixth week) reacted to the Mantoux test in 94.2 per cent of the cases and 98.6 per cent to killed BCG vaccine. Children who had been vaccinated orally were tested fourteen weeks after the last oral dose. The conversion rate was 95.3 per cent among 1,128 children tested with killed BCG vaccine and 85.3 per cent among 1,022 children

subjected to the Mantoux test with O.T. Among 268 tested with the scarification method with O.T., the rate was only 65.1 per cent.

There is no question that the significance of the tuberculin test has become much greater. Forman,[84] in his article on the present value of the tuberculin test, notes that in his student days (1909-1913), approximately 70 per cent of school children had positive tuberculin tests, whereas today only about 5 per cent are positive. He also comments that a positive skin test in the absence of clinically active tuberculosis does not mean the patient has become immune and is therefore protected against the disease. He points out that recent military experience has taught us that recruits having a positive test did develop tuberculosis five times more frequently than did the ones with negative tests.

One of the pitfalls in the past, according to Forman, has been the fault of reading the test too closely. The induration from the test should measure 10 mm and not 5 mm in diameter. Since it is now generally believed that repeated tests in a non-reading person will not sensitize or light up an active lesion that was inactive, Forman recommends that the tuberculin test be a part of systematic investigation of all lung complaints. "While positive reactions occur more frequently with the patch, the intradermal test is more accurate since the measurer dose of tuberculin is introduced."

Ito[85] made in Japan an extensive study of the delayed tuberculin reaction in infants and children. He found delayed reactions, as is to be expected, more frequent among older children. The number of reactions was highest on the third day after a tuberculin injection. He also found a higher rate of reactions in BCG-vaccinated persons.

Unfortunately, despite the thorough work of the World Health Organization to establish international standards for tuberculin, the problems of a uniform tuberculin to be used all over the world are not yet solved. Judging by the literature, by using synthetic medium tuberculin and putting it through various processes, such as ultra filtration for example, we are obtaining more uniform testing material even though the ideal goal is as yet unachieved. It seems that with a heat-concentrated synthetic medium, fewer non-specific reactions occur. This was also the case in animal experimentation. Berg[86] found that with Old Tuberculin he could only determine active infection in 15 per cent of the dogs tested intradermally when giving a dose of 1,500 international units. Using 5,000 units, positive reactions were elicited in 50 per cent of the tuberculous animals. He therefore concluded that, at least in dogs, Old Tuberculin was not reliable for diagnosing tuberculosis. When he used a heat-concentrated synthetic medium, fewer non-specific reactions occurred.

Mitchell and Jackson[87] gave school children between ten and fifteen years of age simultaneously an intradermal tuberculin test using PPD and the Heaf test, using Heaf's multiple puncture apparatus. They found the reading of the Heaf test on the seventh day just as reliable, and perhaps preferable, to earlier readings. Since this is cheaper for mass work than intradermal tests with PPD, they recommended this method.

Japanese investigators[88] have noticed that, since the war, "the accelerated phenomenon of the tuberculin reaction at the customary application site has been markedly enhanced." They assume this is due to the repeated injections of tuberculin incidental to the propagation of BCG. In the last few years, the acceleration of the tuberculin reaction has become so significant in Japan that many more false readings were noted.

Ikegami[89] suggests that, for people who have had the tuberculin test, a

different site should be used three years later when testing—thus avoiding some of the false readings.

The present progress in the control of tuberculosis is temporarily paradoxical.[90] The death rate has fallen to 8.41 per 100,000 for the nation. The incidence of new cases lags far behind the death rate. But the morbidity is high, with 69,000 new cases reported yearly, and costing the United States government more than eight million dollars a year. Considerable interest is being given therefore to the value of the tuberculin test. Badger, in his review of the progress in tuberculosis,[90] reports that at the meeting of the Skin Testing Committee of the American Trudeau Society and the National Tuberculosis Association held in St. Louis in 1959, opinion was divided in some areas on the interpretation of the intradermal tuberculin skin test. Unofficially, the discussion and accord took the following direction: The purified protein derivative (PPD) is the tuberculin of choice. The intracutaneous Mantoux test is the method of choice. Old Tuberculin, however, may be used instead.

For case finding and diagnostic work and after BCG vaccination, 5 tuberculin units (5 T.U.) is recommended as the standard single dose with PPD or O.T. For individual diagnostic work a tuberculin dilution stronger than the intermediate strength should be available. Those wishing to eliminate tuberculosis as a consideration in differential diagnosis by evidence of a definitely negative tuberculin skin test, should use the second-strength PPD, 0.00001 mg, or O.T., 1.0 mg (1:100 dilution) both equivalent to 250 T.U. A skin test showing an induration of 10 mm or more in the intermediate 5 T.U. strength should be considered as a well defined positive test. A 6-9 mm induration is in the area of uncertainty and disagreement in interpretation. The World Health Association presently is studying an intermediate strength of PPD tuberculin with Tween-80 added to prevent glass adsorption.

Badger concludes that the practical usefulness of intradermal skin testing with 0.1 ml of the intermediate-strength PPD or O.T. "will eliminate a large number of false-positive reactors and pick up almost all the cases of tuberculosis."

Experimental Studies on Tuberculin Allergies.—Waksman challenged the assumption that tuberculin sensitivity regularly follows contact of the sensitive cells with the antigen (tuberculoprotein). He and Matoltsy[91] devised new techniques and demonstrated that washed sensitive peritoneal exudate cells when brought in contact with antigen could survive and had a tendency to mature into macrophage type cells. This did not occur in the absence of antigen. Washed peritoneal exudate cells from tuberculin-sensitive guinea pigs and those of normal control animals were kept at 37° C in standing tubes in a culture medium of 20 per cent normal homologous serum and various concentrations of Old Tuberculin, PPD and glycerine. Total viable cell counts, staining and differential counts were done. The tubes containing antigen showed a slight fall in total cell count during the first eighteen hours. Seventy-two to ninety hours later there was a marked rise when compared to the control cells without antigen. The cells treated with antigen showed a greater tendency to survive as compared to the control cells. The large macrophages which were present at the beginning would have a tendency to disappear. In the later stages, the "intermediate mononuclear" cells would mature more quickly to large macrophages.

These two investigators also did some quantitative studies of local passive transfer of tuberculin sensitivity with peritoneal exudate cells in the guinea

pig.[92] They mixed such cells with antigen and injected it into the skins of normal guinea pigs. Typical tuberculin reactions were elicited using the intracutaneous injection of the antigen-sensitive cell mixtures. They also succeeded in producing with intracorneal injections, opacities which lasted from forty-eight to seventy-two hours. Control mixtures failed to produce the same phenomena. Newborn recipients failed to show local passive skin reaction. High concentrations of tuberculin, such as 1:5, would frequently inhibit the transfer phenomenon. Cells incubated in the presence or absence of antigen gave negative transfers. The antigen-sensitive cell reaction at the transfer site gave an increase in the volume of cells observed in the experiments on the effect of tuberculin on peritoneal cells of sensitized guinea pigs in surviving cell cultures. This, Waksman and Matoltsy believe, may account for the size of the local reactions in the absence of participation of the cells of the recipient.

It is to be hoped that more experimental work will be done along these lines, since Waksman's and Matoltsy's experiments have great potentialities as a tool to help us clarify some of these as yet very controversial immunonologic dynamics.

Kosaki[93] reported in 1957 the close relationship between tuberculin hypersensitivity and mononuclear cells. He studied in detail the reaction by means of cellular passive transfer, especially the cells to be transferred in the quantity necessary for the establishment of the reaction. He found that tuberculin hypersensitivity can be transferred passively with peritoneal exudate cells, spleen, and liver homogenates. The mononuclear cells and not the granulocytes are responsible for successfully transferring tuberculin hypersensitivity. He was able to effect passive transfer by injecting cells intraperitoneally, as well as intradermally, using the Prausnitz-Kuester technique. The intensity of transfer tuberculin sensitivity depended mostly upon the quantity of cells used. He also found[94] that the intensity of transfer tuberculin sensitivity depends mainly upon the reactivity of the donors. This same investigator also studied the local reaction or relation to tuberculin sensitized cells[95] and found that when mixing tuberculin with serum from guinea pigs and injecting this into normal and tuberculous guinea pigs, no dermal response or decrease of the tuberculin potency could be noted, as was the case when using tuberculin mixed with normal guinea pig serum.

Erythema and induration took place at the site of the injection of tuberculin in normal guinea pigs. The author found that the potency of the tuberculin, if assayed after the removal of added cells by centrifugation, decreased. Neither a dermal response nor a decrease of potency of tuberculin was observed when tuberculin had been mixed with cells derived from normal guinea pigs.

The relation of hypergammaglobulinemia to necrosis in tuberculin sensitivity was studied by Favour.[96]

Guinea pigs vaccinated with killed tubercle bacilli vary greatly in their capacity for developing and maintaining hypersensitivity. When 1 mg bacilli in oil is given twice in a month, maximal hypersensitivity develops after two months. When three weekly 10 mg doses of vaccine are given, maximal hypersensitivity appears later.

Maximal hyperglobulinemia, if present, generally is present at the same time there is hypersensitivity with the 1 mg dose, and occurs later with the 10 mg dosage. But both groups of animals developing hypergammaglobulinemia, also develop necrotic areas, 4 mm in diameter, in tuberculin skin tests (5 mg PPD) and will have stunting of their growth. The first sign of these skin test reactions is a six to eight-hour delayed one, and is the same

irrespective of whether necrosis develops later. Some animals with hypergammaglobulinemia showed weight loss and tuberculin anergy late in the course of immunization. Favour finds that these findings are consistent with the hypothesis that "this method of sensitization necrosis in classic tuberculin reactions is due to an Arthus-type hypersensitivity, superimposed on and triggered off, by a less intense delayed-type response."

Apparently, tuberculous antibodies in the maternal sera can be transmitted through the placental barrier mainly in the form of incomplete antibodies.[97]

Studies carried out by Mead and his group,[98] on vaccinated guinea pigs with varying doses of BCG showed that when these animals were challenged with 0.01 mg of virulent tubercle bacilli, together with non-vaccinated animals, and then two weeks following infection the animals received 5 mg daily isoniazid for two weeks, the BCG vaccinated animals showed an evident immunity compared with the control animals.

F. Laborie and R. Laborie[99] for several years studied the antigen-antibody relationship in man and animals in tuberculin microbial alimentary and chemical allergies. They employed modern bioelectrometrical techniques in their work. They found that: (1) there is a significant rise in gammaglobulin in tuberculin and microbial allergy; (2) in the alimentary allergy, only a marked rise in gammaglobulin occurs; (3) every experimental application of antigen or specific allergen automatically produced within a few hours an increase in betaglobulins. Clinically, there was simultaneously a temperature rise in tuberculin and microbial allergy; (4) the application of antigen or allergen caused other phenomena in addition to the betaglobulin rise, such as serological metabolic modifications in the level of glycogenesis, cholesterogenesis, azotaemia, serum lipase, pH and hemic oxydo-reduction potential.

Hall and Scherago[100] took a group of guinea pigs and experimentally infected them with *Mycobacterium tuberculosis* H37Rv. They were skin and leukocytic sensitive. After being treated with streptomycin and isoniazid it was found that as the disease became inactive, the leukocytic sensitivity disappeared although the skin sensitivity remained.

Hungarian scientists[101] have been studying the mechanisms of descoccogenic complex antigen formation and their staphylogenic sensitization. Coccogenic complex allergens, which could be considered as "auto antigens" of the skin, were prepared by using *Staphylococcus aureus* strains mixed with skin proteins or with amino acids of the skin. The filtrates of these strains were grown and incubated with "skin materials" (epidermis, corneum) and two different kinds of amino acid mixtures, the albumin and globulin.

Sensitizing experiments were carried out on human skin: twenty-seven of the forty-eight individuals tested gave positive skin reactions. "Inverse positive transfers" were done on the series of sensitized patients. Positive results were obtained in twenty-three instances. It was believed that both the immediate and delayed reactions could be explained on the basis of the mutual amino-acid contents of the carrier substances.

Hall and his co-workers,[102] using a leukocyte migration technique, tested for sensitivity the leukocytes of apparently normal and clinically allergic subjects to filtrates of broth cultures of fourteen species of microorganisms. They found the incidence of sensitivity to be from 1.3 to 8.3 times greater among clinically allergic subjects than among the normal, depending on the species of the microorganism.

Johanovsky[103] (Prague) has extended the studies on the formation of

pyrogenic substances by incubation of cells from BCG-sensitized rabbits with tuberculin *in vitro*. He used two different systems of delayed hypersensitivity: (1) hypersensitivity induced by BCG infection and (2) by means of precipitates of diphtheria toxoid with antitoxin.

Spleen and lymph node cells were incubated *in vitro* with diluted tuberculin, diphtheria toxoid, and Hanks solution. Supernatant fluids obtained after various incubation periods were tested in normal, non-hyposensitive guinea pigs for pyrogenic activity and the capacity to induce skin inflammatory reactions.

Johanovsky obtained pyrogenic substances in most of the experiments in which cells of hyposensitive guinea pigs were incubated with the specific antigen. Experiments with the unrelated antigen and controls were negative. He found the formation of skin-irritating substances to be not so regular and sometimes they were formed non-specifically in control experiments. In principle, however, these experiments showed conformance with the results of the fever reaction. In other experiments, he studied the effect of mixing and incubating hyposensitive cells *in vitro* with the corresponding antigen on the ability of these cells to transfer passively skin and systemic hyposensitivity to normal recipients.

Clinical and Immunobiological Studies in Connection with Tuberculin Treatment.—For the past six years, Rusti,[104] a very earnest European worker, has been studying the ease of attaining natural immunity in tuberculosis—as he terms it, the biological way of treatment—by carefully evaluating treatments performed with tuberculin. He found that in the tuberculous patient, tuberculin allergy can be artificially changed. Giving subcutaneous tuberculin injections in precise doses may change the state of sensitivity into a state of insensitivity. Such an altered condition, that is, the enhanced tuberculin resistance, is therapeutically of the greatest importance and, in Rusti's opinion, is due to the presence of an anti-allergic antibody. When tuberculin treatment is discontinued, this enhanced resistance can be maintained only for a short period of time, but can again be brought about by resuming treatment. Some of his experiments seem to support the existence of a hypothetic anti-allergic antibody. In high tuberculin resistance attained through artificial desensitization, the organism reacts at the site of the tuberculin injection with the formation of real granulation tissue, that is, an abacillary tubercle.

DELAYED REACTION

The delayed allergic reaction plays an important role in orienting the host's response in bacterial, fungal, and viral infections, which can be seen most readily in those diseases with a chronic course and a granulomatous inflammatory response. Although there seems to be a marked similarity between the details of changes in delayed allergic responses and in the so-called collagen diseases, there is still no agreement as to whether or not these collagen diseases have a microbial hypersensitivity etiology. The delayed reaction is distinct among the types of allergic responses, as the allergy developed is highly specific. No measurable serum antibodies have yet been demonstrated, but antibodies do appear and become part of the host's tissues. This has been proven by transferring sensitivity with washed blood cells from the circulating blood, lymph nodes, or splenic extracts. The cellular transfer of delayed hypersensitivity has become one of the most important tools for studying the mechanism involved, and Lawrence and others not only have shown that the leukocytic factor involved in this transfer may

be extracted from cells by lysis or freezing-thawing, but also that it is stable for eight hours at 25° C and may be frozen for six months. Moreover, not only is this transfer factor unaffected by deoxyribonuclease, ribonuclease, or trypsin, but it is apparently species-specific as well.

The transfer of delayed tuberculin and diphtheria toxoid sensitivity[105] has been successfully carried out using DNAse-treated leukocyte extracts. No antibody of the conventional type was detected in these extracts, nor in the sera or skin of recipients when maximum transferred toxoid sensitivity existed. This finding suggests that antibody of the conventional type is not transferred. Merely upon incubation, the transfer factor may be released from viable cells, since incubation[106] of viable, sensitive leukocytes in the presence of tuberculin (PPD) desensitizes the cells and liberates a transfer factor into supernatants. Lawrence[106] points out, however, that "the possibility of a primary toxic effect of contaminating material in PPD preparation cannot be excluded." Delayed coccidiodin sensitivity can also be transferred with DNAse-treated leukocyte extracts, and transferred sensitivity may persist up to one and one-half years without antigenic exposure. Nonsensitive leukocyte extracts incubated with antigen do not confer sensitivity, which, according to Lawrence, suggests that "endowment of recipients with *de novo* sensitivity transfer is probably not due to antigen in extracts and role of exposure to antigen in duration of transferred sensitivity is not necessarily causal."

It is well known that the antigens associated with bacteria do not necessarily exist in a disperse state throughout the microorganism, but may be found in layers or strata. Such examples of antigen stratification occur with pneumococci, streptococci and salmonella. Several years ago, Meynell[107] reported that the superficial antigens of a strain of tubercle bacilli of human origin appear to be polysaccharides, while those more deeply situated are protein.

Since simple water or saline extraction removes erythrocyte-sensitizing substances from non-defatted mycobacteria, Thurston and Rheins[108] decided to determine whether repeated extraction of the same bacillary mass would result in antigens with different specificities. Then, these differences might be correlated with the relative solubilities and position of the antigens in the bacterial cell. By repeated extraction of BCG cells, they obtained erythrocyte-sensitizing antigens and found that the arrrangement or solubility of these antigens in BCG seemed to differ from those of *M. phlei.* Their conclusion was that "the technique of repeated extraction of the same bacillary mass offers a method of investigating various mycobacterial antigen-antibody systems."

Another example of this sort was provided by Cummings and his collaborators[109] who worked with the passive transfer of tuberculin hypersensitivity without intact viable cells. First, using cells of peritoneal exudates or spleen homogenates from sensitized donor guinea pigs, they lysed the cells by sonic vibration; then, using an extract, they were able to passively transfer tuberculin hypersensitivity to normal recipient animals. These experiments suggest that the material responsible for passive transfer may possibly lie in the sensitized donor's cells, and Cummings and his group believe that the active principle may be similar to the antibody described by Cole and Favour[110] in their plasma fraction IV-10 obtained from sensitized guinea pigs. These authors demonstrated that the antibody to tuberculoprotein resides entirely in a newly discovered plasma fraction called IV-10, which is part of Cohn's fraction IV (alpha globulin) and fraction V (albumin). When obtained from sensitized guinea pigs, fraction IV-10 will passively transfer to normal guinea pigs a delayed skin sensitivity to PPD tuberculin.

In a later article, Favour[39,40] emphasizes that "*in vitro* methods for studying delayed type allergy are inconclusive evidence for generalized host-cell sensitivity in delayed-type reactions." He also feels that:

> The plasma-cell gamma systems play no part in the delayed reaction. Under ordinary circumstances, delayed-type reactivity is an active process dependent on viable cells derived from lymph nodes, spleen, the peripheral blood or of the cells which constitute a part of the inflammatory granuloma bout tissue deposits of sensitizing agents.

Animal experiments, according to Favour, seem to point to some relation between the duration and the existence of survival of these lymphoid elements in the sensitized animal.

Lack[111] studied the changes in the omentum of guinea pigs and rabbits, following intraperitoneal inoculation of *M. tuberculosis,* H37 Rv, H37 Ra, BCG, *M. smegmatis, M. phlei,* and an unspecified microbacterial strain obtained from tap water. An invasion of lymphocytes occurred when there was hypersensitivity in the primary infection and two days after secondary infection. Lack implies that cell density of tubercles might hinder bacillary multiplication and that ensuing necrosis comes from a combination of antigens released from bacilli with antibodies carried by lymphocytes. On the basis of his findings, Lack offers the following hypothesis:

> In primary infection, the avirulent strains do not survive long enough to sensitize the host under the conditions of the experiment. BCG and H37 Rv do multiply sufficiently to provide enough antigen for sensitization. Antibodies carried by lymphocytes increase in number as more bacilli are destroyed and more antigen is released. The invasion of the lymphocytes itself increases the rate of destruction of bacilli by increasing the density of the tubercle. The caseation of the thirty-second day omentum appears to be an extension of this process.

Favour admits that even though the lymphoid cell is capable of transferring the delayed-type reactivity, we still do not know the mechanism responsible for this. "It will be apparent that many fundamental enigmas still plague the serious student of delayed-type tuberculin allergy." He also feels that "a variable portion of the tissue reaction is due to accompanying anaphylactic-type responses."

Charpy[112] believes that the different types of delayed allergies are produced by various combinations of antigens (chemical, soluble microbial products, fungal or viral, et cetera) inside of various organ tissues, with proteins liberated by the host's tissues. Each time that such an antigen mixture is formed in a tissue, it is probably absorbed by the lymphatic and forms globulin antibody. According to Cushing and Campbell,[12] the difference between the delayed reaction and the classical anaphylaxis may be merely "quantitative because of the nature of the antigens involved and the presence of antigen in the hypersensitive animal." More study is needed on the problem of hypersensitivity to infectious agents before we can determine whether hypersensitivity to agents is fundamentally unique and different from the classical antigen-antibody mechanism of anaphylaxis.

By washing leukocytes from inflammatory exudates, buffy coats, spleens, or lymph nodes, Chase[23,25] succeeded in transferring the delayed type of dermal sensitivity to tuberculin to unsensitized guinea pigs. The process takes place only when the cells are viable. Lawrence believes that "this fundamental contribution provides the most direct evidence to date that tuberculin sensitivity is probably mediated by an immune mechanism intimately bound to the cells and is not the result of some nonspecific response."[113] Kircheimer, Weiser, and Van Liew[114] have also shown that a cellular transfer

from a tuberculous animal can cause a systemic reaction to tuberculin in the recipient. In another instance of bacterial hypersensitivity, Mataxas-Buehler[115] and Carrére and Quatrefages[45,116] independently showed that Brucella sensitization of the guinea pig was also transferred from cells.

Raffel[26] suggests that in bacterial allergy "cells may transfer an already existing state to a recipient. who, because of lack of elements essential for completing the synthesis of humoral antibodies, is incapable of carrying this process forward." He also warns not to make the assumption that agammaglobulinemic patients cannot develop bacterial hypersensitivity, because he knows of two cases in which the patients had positive reactivity to tuberculin. "It would seem wise, for the present, to leave the decision open pending more information."

In their classic 1932 paper, Rich and Lewis[117] showed that tissue cultures of sensitized cells (polymorphonuclear leukocytes, mononuclear phagocytes, lymphocytes, immature cells of the bone marrow and connective tissue cells) are killed by amounts of tuberculin filtrate which are harmless to similar cells from normal animals. The usual assumption has been that there is a general tissue reactivity of the delayed type, and the cells involved are not restricted to any particular type. Much work done since then points to the same conclusions.

Despite all of this work, however, none of these studies proves which cells are responsible for establishing the hypersensitive state, nor which cells are responsible for antibody formation. According to Rich,[7] "it is unlikely that the production of antibody is a function of all cells," and he agrees with those investigators who are of the opinion that probably the cells producing antibodies give reactivity to other tissue by liberating their own antibodies or by themselves producing antigens in areas where the test injection is positive.

DELAYED HYPERSENSITIVITY AND AGAMMAGLOBULINEMIA

Agammaglobulinemic patients, whether congenital or acquired, are prone to bacterial infections and show an almost complete absence of gammaglobulin in their serum. No antibodies can be demonstrated in their blood or tissues, and even under antigenic stimulation, they do not form antibodies. Good and his associates[118] have thoroughly studied delayed hypersensitivity in agammaglobulinemia and have shown that patients with this disease, when properly stimulated, can regularly be made to develop delayed allergy "even without antibody formation." They also can develop delayed allergy during the natural course of infections, as was demonstrated by the natural development of tuberculin sensitivity, as well as after BCG infection. There is even a case on record[119] of sensitivity developing after a histoplasmosis infection. The observation that such patients, although suffering from a marked disturbance in the immune response, retain their capacity to develop delayed allergy has led many investigators to believe that delayed allergy has a different mechanism than that of the classical immune response, where circulating antibody and gammaglobulin is formed.

Since agammaglobulinemic patients develop immunity to re-infection after certain viral diseases, Good and his group[118] suggest that perhaps this form of immunity is a type of primitive immune response which can produce a delayed hypersensitivity and is retained by these patients to a marked degree. Since these same patients retain the immunologic capacity to develop delayed allergy and resist virus infections, the question arises why they do not develop delayed allergy to streptococcal and pneumococcal products after infections with these microorganisms. Good and his co-

workers give the explanation that, because of the incapacity of these patients for serologic resistance, their survival when infected with one of the extracellular pathogens necessitates antibiotic treatment that results in the elimination of these organisms from the tissues. This prevents the development of delayed allergy to these organisms. It is well known that fibrinoid diseases occur quite often among agammaglobulinemic patients, and there is sufficient evidence to suspect that rheumatoid arthritis and other fibrinoid diseases in such patients are the result of delayed allergy rather than classical immunity. According to Good and his group, their observations agree with Pappenheimer's theory that delayed allergy is a stage in the development of classical immunity and antibody production, and that agammaglobulinemic patients can initiate, but not complete, the immune response.

HORMONAL AND NUTRITIONAL FACTORS IN BACTERIAL ALLERGY

Bacterial allergens, like bacterial toxins, can produce nonspecific trauma according to Long.[120] Intradermal injection of tuberculin into guinea pigs will, several days later, precipitate acute protein deficiency which had been subclinical. Long believes that hypersensitivity to bacterial allergens induces a strain on protein metabolism. "Nutritional and hormonal factors may influence immune or allergic responses to infection, either because they are present from the onset of the disease, or because they are the consequence of infection. Endocrine imbalance or nutritional deficiency may be a nonspecific sequel to bacterial stress."

On the basis of his experiments, Long concludes that there is a clear-cut species difference in susceptibility to delayed bacterial allergy of the tuberculin type, in resistance to cortisone, in inability to synthesize ascorbic acid, and in the nonprotein SH content of the carcass. The ratio of insulin to cortisone output has considerable influence on the immune and allergic responses of guinea pigs to bacterial antigens. On the other hand, he believes that the rôle of hormones upon sensitivity to tuberculin is intimately associated with ascorbic acid-sulfhydryl metabolism.

ANAPHYLAXIS

Some interesting experiments were reported by Stone and Freund.[121] They sensitized guinea pigs to egg albumin intracutaneously with the aid of paraffin oil adjuvants having mycobacteria. When large doses were given, the animals developed massive hemorrhagic reactions at the injection sites. This did not occur, however, when mycobacteria was omitted, despite the fact that such animals developed high antibody titers and had systemic reactions. Because mycobacteria are necessary for producing the hemorrhagic reactions, it was suggested that this may be a delayed-type sensitivity. The mechanism which produces the hemorrhage is still unknown, but these experiments seem to show that antibody titers and anaphylactic sensitivity are not the decisive factors.

Tuberculous guinea pigs develop hemorrhagic reactions at the sites of intracutaneous tests with tuberculin following intravascular injections of *S. typhosa* or *E. coli* endotoxins. Stone and Freund[121] attempted to determine if this hemorrhagic phenomenon was similar to the one found in relation to protracted anaphylactic shock. They skin tested with PPD animals that had been sensitized with adjuvants containing *M. tuberculosis*. Protracted anaphylactic shock was induced in these animals. Gross hemorrhages did not occur at the sites of the tuberculin reactions. They did occur, however, at the tuberculin sites following intravenous administration of endotoxins.

It has been observed that, in anaphylaxis studies in the guinea pig, occasionally the control animals were protected against anaphylaxis. Feinberg and his group[122] inhibited anaphylaxis in the guinea pig by the production of a local abscess in the axilla. In man, there often is a partial or complete remission of allergic symptoms following an acute infection or other conditions frequently labeled as "stress." Some of these are believed to be due to pituitary-adrenal stimulation. The fact that steroids are frequently effective in ameliorating allergic conditions suggests that increased steroid hormone production may be responsible for reduction of hypersensitivity during infection. Feinberg and his colleagues therefore undertook a study to see what effect bilateral adrenalectomy would have on the protection of the guinea pig against anaphylaxis after infection with hemolytic streptococcus. They found: (1) Guinea pigs infected locally with a group C streptococcus developed refractoriness to anaphylaxis following a suitable induction period. Bilateral adrenalectomy after infection but forty-eight hours before challenge did not influence the manifestation of hyporesponsiveness. (2) Surgical trauma did not reduce passively induced hypersensitivity. (3) Infection in adrenalectomized animals failed to alter histamine sensitivity to the tissues.

Since an eight to eleven-day period was necessary for inhibition after a first infection, and only five or less days were necessary after reinfection, these investigators suggest that antibody production may be a factor. However, presently we do not know the exact mechanism by which clinical or experimental infection alters hypersensitivity.

A serum factor according to Feinberg and co-workers[123] seems to be involved in the inhibition produced by an extraneous antigen-antibody reaction since the protection by unrelated antigen and antibody can be reserved by the injection of fresh serum. They believe that this serum factor is not serum complement.

Sanyal[124] successfully produced anaphylactic shock in the rat by injecting *Haemophilus pertussis* vaccine, containing the organisms in the smooth phase, along with a sensitizing dose of foreign protein. Re-injection later of the foreign protein alone, leads to progressive shock which is fatal in most of the animals. There is a fall in blood pressure when rats suffer from anaphylactic shock. Animals sensitized only with foreign protein show only a transient drop in blood pressure. When *H. Pertussis* is used with the foreign protein, the fall in blood pressure is prolonged.

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580 Doctors Building

(To be continued)